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(54) Title: NOVEL CHELATING LIGANDS HAVING A TRIPODAL BACKBONE			
(57) Abstract <p>The invention relates to novel chelating ligands which incorporate a tripodal backbone. More particularly, the invention pertains to novel tripodal ligands which form coordination compounds with a variety of metal ions, particularly, but not exclusively, trivalent metal ions and lanthanide metal ions, which are useful in nuclear medicine. A novel amine phosphinate tripodal ligand, a chelating ligand and a process therefor involving a metal ion and particularly a trivalent metal ion of the group 13 metals and the rare earths. The process comprises complexing Tc or Re or any one of the group 13 metals, Al, Ga and In, and any one of the rare earths, Sc, Y, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, with an amine phosphinate tripodal ligand.</p>			

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NOVEL CHELATING LIGANDS **HAVING A TRIPODAL BACKBONE**

FIELD OF THE INVENTION

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The invention relates to novel chelating ligands which incorporate a tripodal backbone. More particularly, the invention pertains to novel tripodal ligands which form coordination compounds with a variety of metal ions, particularly, but not exclusively, trivalent metal ions of the group 13 metals and lanthanide metal ions, which are useful in nuclear medicine.

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BACKGROUND OF THE INVENTION

In recent years, vigorous research activity has been conducted to identify and synthesize suitable chelating agents for metal ions and particularly trivalent metal ions such as the group 13 metals and the lanthanides, for use in nuclear medicine. This is because of the deleterious effects of these metals (e.g. concern over aluminum neurotoxicity) and their burgeoning use *in vivo* as diagnostic probes. For example, gallium and indium radionuclides are used in radiopharmaceuticals. Further, the physical properties of the lanthanides are exploited as luminescent, EPR, and NMR shift probes. They also have widespread application as magnetic resonance imaging contrast agents. Similarities in oxophilicity (e.g. Al(III), Ln(III) and ionic radii (e.g. In(III), Ln(III)) do not necessarily result in a complementary chemistry for the respective group 13 and lanthanide ions.

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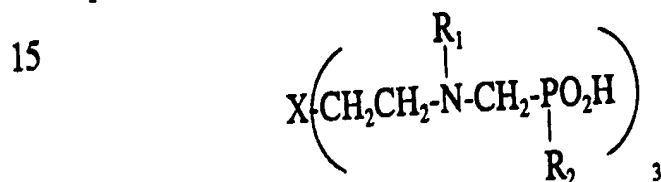
SUMMARY OF THE INVENTION

The invention relates to novel compositions of matter, a process for preparing these novel compositions of matter, a new series of chelating ligands, and a series of their metal complexes, which have use in diagnostic and therapeutic nuclear medicine.

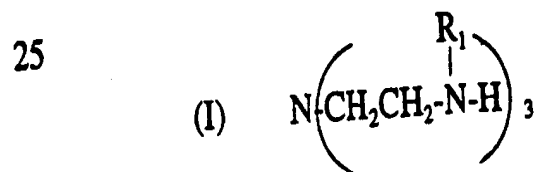
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wherein X is N, CH, C₂H₃, C₃H₅, or other alkyl, substituted alkyl, or
 or benzyl; and when X is N, R₂ is CH₃, CH₂OH, other alkyl, substituted alkyl, or
 aryl, and when X is CH, C₂H₃, C₃H₅, or other alkyl, R₂ is C₆H₅, CH₃, CH₂OH, other
 10 alkyl, substituted alkyl, or aryl, and physiologically compatible salts and derivatives
 thereof.

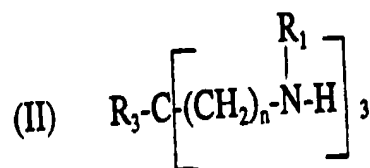
The invention is also directed to a process of preparing an amine
 phosphinate tripodal ligand of the formula:



wherein X is N, CH, C₂H₃, C₃H₅, or other alkyl, R₁ is H, CH₃, C₂H₅ or other alkyl
 20 or benzyl; and when X is N, R₂ is CH₃, CH₂OH, other alkyl, substituted alkyl, or
 aryl, and when X is CH, C₂H₃, C₃H₅, or other alkyl, R₂ is C₆H₅, CH₃, CH₂OH, other
 alkyl, substituted alkyl, or aryl, and physiologically compatible salts and derivatives
 thereof, which comprises (a) reacting an appropriate tripodal amine of the formula:



or

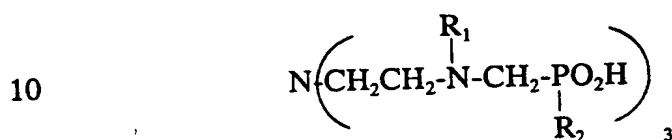


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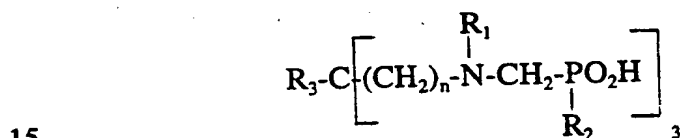
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wherein n is 1 or 2, R₁ is H, CH₃, C₂H₅, or other alkyl or benzyl; and R₃ is H, CH₃, C₂H₅, or other alkyl; with H₂P(R₂)O₂ and CH₂O or (CH₂O)_m, wherein R₂ is H, C₆H₅, CH₃, other alkyl, substituted alkyl, or aryl, excepting R₂ is C₆H₅ for compound (I), and m is 2 or greater; or (b) converting the R₂ group of one amine phosphinate tripodal ligand to another R₂ group by using formaldehyde or paraformaldehyde.

The invention is also directed to a process of preparing an amine phosphinate tripodal ligand of the formula:



or



wherein n is 1 or 2, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and R₃ is H, CH₃, C₂H₅, or other alkyl; and R₂ is CH₂OH, and physiologically compatible salts and derivatives thereof, which comprises converting an amine phosphinate tripodal ligand wherein R₂ is H to an amine phosphinate tripodal ligand wherein R₂ is CH₂OH by reacting with formaldehyde or paraformaldehyde.

The invention is also directed to a process of chelating a metal ion with an aminophosphinate tripodal ligand according to the invention. The invention is also directed to a process of chelating a trivalent metal ion such as Technetium (Tc) or Rhenium (Re) or a trivalent metal ion of the group 13 metals and the rare earths which comprise complexing any one of the group 13 metals, Al, Ga and In, and any one of the rare earths or lanthanides, Sc, Y, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, with the amine phosphinate tripodal ligand, according to the invention.

In the process of the invention, any one of the group 13 metals, Al, Ga and In can be complexed with the amine phosphinate tripodal ligand according to the invention or any one of the rare earth metals, Sc, Y, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, can be complexed with the amine phosphinate tripodal ligand according to the invention. The invention also includes the chelation of Beta emitting radioactive isotopes as therapeutic agents, including but not limited to the isotopes Sm 153, Ho 166, Y 90, Pm 149, Pr 145, Dy 166, Ln 177 and Yb, and for imaging applications including but not limited to In 111.

The invention is also directed to a chelate comprising a complex of a metal ion or a trivalent metal ion such as Tc or Re or a trivalent metal ion of the group 13 metals, Al, Ga and In, and the rare earths, Sc, Y, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu and the amine phosphinate tripodal ligand according to the invention. The complex can be a group 13 metal complex and the metal can be selected from the group consisting of Al, Ga and In or the complex can be a rare earth complex, including Sc and Y, and the lanthanide can be selected from the group consisting of La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu.

BRIEF DESCRIPTION OF DRAWINGS

In drawings which illustrate specific embodiments of the invention, but which should not be construed as restricting the spirit or scope of the invention in any way:

Figure 1 depicts an ORTEP representation of the cation in $[\text{Lu}(\text{H}_3\text{ppma})_2](\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$ (25% probability thermal ellipsoids). Only one phenyl group is shown for clarity.

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Figure 2 depicts an ORTEP representation of the cation in $[\text{Lu}(\text{H}_3\text{ppma})_2](\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$ (25 % probability thermal ellipsoids). View approximately down the threefold axis.

5 Figures 3(a) and 3(b) represent experimental lanthanide titration curves at 2 mM H_6tams : 2 mM $\text{Ln}(\text{III})$ (top) and 2 mM H_6taps : 2 mM $\text{Ln}(\text{III})$ (bottom). a = moles of NaOH /moles of ligand.

10 Figures 4(a) and 4(b) represent experimental plots of \bar{n} (the ratio of bound ligand to total metal ion concentration) vs. $\log [\text{tams}^6]$ (top) and \bar{n} vs. $\log [\text{taps}^6]$ (bottom); the solid lines were generated using the calculated stability constants, $K_{\text{Ln}(\text{tams})}$ and $K_{\text{Ln}(\text{taps})}$.

15 Figure 5 illustrates ^{31}P (121.0 MHz) NMR spectrum for the stability constant study of the $\text{Yb}(\text{III})/\text{H}_3\text{ppma}$ system, $R = [\text{L}]_{\text{T}}/[\text{M}]_{\text{T}} = 3.8$.

 Figure 6 illustrates a plot of \bar{n} vs. $[\text{H}_3\text{ppma}]$ for the $\text{Yb}(\text{III})$ (\circ) and $\text{Lu}(\text{III})$ (\square) systems (solid lines indicate fits, symbols indicate experimental data). The calculated curves for the group 13 metal ions⁸ are included for comparison.

20 Figure 7 illustrates ^1H NMR spectrum (300.0 MHz) of $[\text{Tm}(\text{H}_3\text{ppma})_2](\text{NO}_3)_3$ in CD_3OD (δ corrected for $\Delta\chi$ the shift due to the bulk magnetic susceptibility). * = solvent.

25 Figures 8(a) and 8(b) depict a plot of Δ/C^{D} vs. $\langle S_z \rangle / C^{\text{D}}$ for the ^1H NMR spectra (top: \bullet = hydrogen H_F , \blacksquare = H_G , and \blacktriangle = H_H) and for the ^{31}P NMR spectra (bottom) of $[\text{Ln}(\text{H}_3\text{ppma})_2]^{3+}$ where $\text{Ln} = \text{Sm} - \text{Lu}$.

30 Figure 9 depicts a plot of Dy.I.S. vs. $[\text{Dy}(\text{III})]$ (mM) for $\text{Dy}_{(\text{aq})}^{3+}$, \blacktriangle , $[\text{Dy}(\text{TAMS})]^{3+}$, \circ , $[\text{Dy}(\text{TAPS})]^{3+}$, \square , and $[\text{Dy}(\text{H}_3\text{TRNS})_2]^{3+}$, \circ . Error bars represent linewidths at half height.

H₃ppma (or H₃trns³⁻) equilibria viewed in terms of hydrophobic interactions.

Figure 11 depicts comparative pM values vs. Z for H₃trns³⁻ ([Ln(III)]_{tot} = 1 mM), \bullet , ([Ln(III)]_{tot} = 1 μ M), \ominus , taps⁶⁻ ([Ln(III)]_{tot} = 1 mM), \blacktriangle , tams⁶⁻ ([Ln(III)]_{tot} = 1 mM), \blacksquare .

Figure 12 illustrates the graphical formulae for H₃ppma, H₆trns, H₆tams and H₆taps.

Figure 13 illustrates a graphical scheme for complexing bicapped, monocapped, and encapsulated configurations.

DETAILED DESCRIPTION OF THE INVENTION

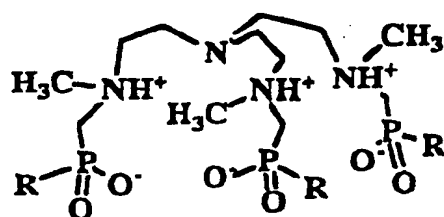
An N₄O₃ tripodal tren-based (aminomethylene)phosphinato ligand tris(4-(phenylphosphinato)-3-methyl-3-azabutyl)amine (H₃ppma) has been synthesized, and its complexation properties with the group 13 metals Al, Ga, and In have been investigated. The molecular structure of the indium complex [In(H₃ppma)₂](NO₃)₃ · 3H₂O (C₆₀H₉₆InN₁₁O₂₄P₆) has been solved by X-ray methods; the complex crystallizes in the trigonal space group R3c, with a = 18.984(3) Å, c = 36.256(5) Å, and Z = 6. The structure was solved by Patterson methods and was refined by full-matrix least-squares procedures to R = 0.040 (R_w = 0.039) for 1415 reflections with I > 3σ(I). The structure of the bis-complex showed the ligand to coordinate in a tridentate manner through the three phosphinate oxygens, resulting in a bicapped octahedral structure of exact S₆ symmetry. The solved structure was of the RRRSSS diastereomer, where half of the molecule contained phosphorus atoms of R chirality and the other half contained phosphorus atoms of S chirality. The highly symmetric environment about the metal atoms produces a low electric field gradient at the metal nucleus leading to unusually narrow line widths in the ²⁷Al, ⁷¹Ga, and ¹¹⁵In NMR spectra. The aluminum complex [Al(H₃ppma)₂](NO₃)₃ · 2H₂O

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exhibited an extremely rare example of aluminum-phosphorus coupling ion both the ^{31}P and ^{27}Al NMR spectra, where $^2J_{\text{AlP}}$ was shown from both spectra to be 6.7 Hz. The narrow line widths made the complexes amenable to stability constant studies via a combination of ^{27}Al , ^{71}Ga , and ^{31}P NMR spectroscopies (25°C). The formation constants for In^{3+} ($\log \beta_2 \geq 5.4$), Ga^{3+} ($\log \beta_2 = 4.24$), and Al^{3+} ($\log \beta_1 = 0.93$, $\log \beta_2 = 3.45$) decrease by an order of magnitude as the group is ascended, consistent with increasing steric interactions of the phenyl groups as the two trisphosphinate ligands are crowded together in order to coordinate the smaller metal ions. Variable temperature ^{27}Al and ^{31}P NMR spectroscopic studies indicated the RRRSSS diastereomer to be rigid up to 55°C in CD_3OD .

The results of this work were published in J. Am. Chem. Soc. 1996, 118, 10446-10456, under the title "Highly Symmetric Group 13 Metal-Phosphinato Complexes: Multinuclear NMR (^{27}Al , ^{31}P , ^{71}Ga) Determination of Stability Constants at Low pH", Mark P. Lowe, Steven J. Rettig, and Chris Orvig. The full disclosure in this article is incorporated in the specification herein by reference.

General Synthesis Procedure. The appropriate tripodal amine (derivatives of tren and tame specifically) are reacted with a suitable phosphinic acid and formaldehyde under Moedritzer-Irani synthesis (Moedritzer, K., Irani, R.R., *J. Org. Chem.* 1966, 31, 1603) conditions as shown below for H_3pma and H_3ppma . The P-H derivatives such as H_3pma can then be used to make further derivatives as is shown below for H_3hpma .



$\text{R} = \text{C}_6\text{H}_5$
 $\text{R} = \text{CH}_2\text{OH}$
 $\text{R} = \text{H}$

H_3ppma
 H_3hpma
 H_3pma

5 solution of tris(3-methyl-3-azabutyl)amine (0.50 g, 2.66 mmol) and 50% H_3PO_2 (1.40 g, 10.61 mmol) in H_2O (7 mL) was heated to 40°C . This amine was synthesized by the reaction of tren with ethylchloroformate followed by the reduction of the resulting carbamate with lithium aluminum hydride to give the tri-N-methylated amine: Schmidt, H., Lensink, C., Xi, S.K., Verkade, J.G.Z. *Anorg. Allg. Chem.* 1989, 578, 75. Paraformaldehyde (0.32 g, 10.67 mmol) was slowly added over 1 hr. The reaction was heated for a further 4 hours and then the solvent removed to yield a colorless oil. The oil was taken up in H_2O (10 mL), loaded onto an anion exchange column (Amberlite IRA 412) and eluted with water to remove any unreacted H_3PO_2 or biproduct ($\text{HOCH}_2\text{PH}(\text{O})\text{OH}$). On removal of the solvent, a colorless oil was obtained of $\text{H}_3\text{pma} \cdot 2\text{HCl} \cdot 4\text{H}_2\text{O}$. Yield = 1.21 g (78%). ^1H NMR (200 MHz, D_2O) pD = 6.83: δ 2.96 (t, 6H, ethylenic CH_2 , $^3J_{\text{HH}} = 6.6$ Hz), 3.30 (t, 6H, ethylenic CH_2 , $^3J_{\text{HH}} = 6.6$ Hz), 2.85 (s, 9H, methyl NCH_3), 3.14 (d, 6H, methylenic NCH_2P , $^2J_{\text{PH}} = 10.5$ Hz), 7.17 (d, 3H, phosphinic PH , $^3J_{\text{PH}} = 540.4$ Hz). $^{31}\text{P}\{\text{H}\}$ (80 MHz, D_2O) pD = 6.83: δ 12.45.

20 **Tris(4-phenylphosphinato-3-methyl-3-azabutyl)amine trihydrochloride monohydrate ($\text{H}_3\text{ppma} \cdot 3\text{HCl} \cdot \text{H}_2\text{O}$).** Phenylphosphinic acid (2.13 g, 14.99 mmol) and tris(3-azabutyl)amine (0.91 g, 4.83 mmol) were dissolved in distilled water (20 mL). After slow addition of 37% HCl (20 mL), the temperature of the stirred solution was raised to reflux ($\approx 110^\circ\text{C}$) and 37% w/w aqueous formaldehyde (2.44 g, 30.09 mmol) was added dropwise over a period of 30 min. The reaction was refluxed for a further 5 hours, after which time the HCl - water solvent mixture was concentrated under vacuum almost to dryness. The resulting syrup was taken up in ethanol (100 mL), and acetone (900 mL) was added to give a cloudy solution which was cooled, then filtered. A white highly hygroscopic powder was obtained; this was taken up in water and the solvent removed once more. Drying under vacuum for 12 hours gave a glassy, slightly hygroscopic solid to yield 2.40 g

(64%); Anal. Calcd (found) for $C_{30}H_{45}N_4O_6P_3 \cdot 3HCl \cdot H_2O$: C, 46.31 (46.58); H, 6.48 (6.48); N, 7.20 (7.31). Potentiometric studies were consistent with this molecular weight. Mass spectrum (+LSIMS): $m/z = 651$ ($[L+1]^+$, $[C_{30}H_{46}N_4O_6P_3]^+$). IR (cm^{-1} , KBr disk): 3410, 2460 (b s, $N-H$, $O-H$), 1645 (w, $N-H$), 1438 (s, $P-Ph$), 1206, 1131, 957 (p-o), 740, 685, 599 ($P-C$, $P-Ph$). UV ($_{max}$, nm ($M^{-1}cm^{-1}$)): pH = 1.5, 258 (1375), 264 (1833), 271 (1512).

Tris(4-hydroxymethylenephosphinato-3-methyl-3-azabutyl)amine (H_3hpma). A stirred solution of $H_3pma \cdot 2HCl \cdot 4H_2O$ (0.22 g, 0.28 mmol) in 6M HCl (20 mL) was heated to reflux. Aqueous 37% formaldehyde (0.25 g, 3.08 mmol) was slowly added over 1 hour. The reaction was heated at reflux overnight and then the solvent removed under vacuum to yield a colorless oil. The oil was taken up in H_2O (10 mL), loaded onto an anion exchange column (Amberlite IRA 412) and eluted with water. On removal of the solvent, a colorless oil was obtained of $H_3hpma \cdot 4HCl \cdot 7H_2O$. 0.387 g was obtained, but there was a lot of HCl and H_2O still present. Potentiometry indicated that 0.387 g contained 0.48 mmol of ligand, therefore $Mw = 792.12$. Mw without HCl or water is 512.42, which leaves an extra 283.41. Potentiometry gives the excess acid as about 4 HCl which means about 7 waters. An alternative method is to do the H_3pma reactions as before and then carry on with more paraformaldehyde at $100^\circ C$ in same solution, i.e. avoid the HCl treatment. After passing through anion exchange, there is .3HCl (from column) and one water c.f. H_3ppma , H_3pma . 1H NMR (200 MHz, D_2O) pD = 7.03: δ 3.00 (t, 6H, ethylenic CH_2), 3.41 (t, 6H, ethylenic CH_2), 2.94 (s, 9H, methyl NCH_3), 3.30 (d, 6H, methylenic NCH_2P , $^2J_{PH} = 8.54$ Hz), 3.68 (d, 6H, hydroxymethylene $HOCH_2P$, $^2J_{PH} = 6.35$ Hz). $^{31}P\{H\}$ (80 MHz, D_2O) pD = 7.03: δ 27.35.

Chelation of metal ions and trivalent metal ions such as Tc and Re and the group 13 metals and the lanthanides with a variety of mixed nitrogen/oxygen donors in amine phosphinate tripodal ligands have been investigated. However, until the water soluble sulphonated analogs have been synthesized to give knowledge about the solution behavior. The coordination mode of the ligand can be metal dependent.

For instance, in aqueous solution H_6trns (see Figure 12) forms bicapped bis(ligand) lanthanide complexes in which bonding is solely through the phenolic oxygens, whereas the $Ga(III)$ and $In(III)$ form 1:1 encapsulated complexes in which bonding occurs with both oxygen and nitrogen donors, while $Al(III)$ does not form a stable complex with H_6trns in aqueous solution. The capped and bicapped lanthanide complexes of H_6trns have 16 membered chelate rings, much larger than the 5 and 6 membered rings in the encapsulated complexes. It has been suggested that there is an effect which predisposes the ligand to a binding posture, for example the inter and intrastrand hydrogen bonding between protonated nitrogens and phenolic oxygens. The hydrogen bonding, coupled with the large chelate ring size, can result in a ligand which suffers little or no strain energy in accommodating different sized lanthanide ions, and thus the changes in stability noted (an unprecedented 5 orders of magnitude increase in stability from Nd - Yb) correlated with the increasing effective nuclear charge.

To gain insight into the aqueous chemistry of H_6trns with the lanthanides, the aqueous lanthanide coordination chemistry of two other smaller tripodal aminephenol ligands, H_6tams and H_6taps (see Figure 12), has been investigated. Should these ligands coordinate in a similar manner as H_6trns^{3-} (bicapped), 14 and 13-membered chelate rings would be formed upon lanthanide coordination. The effect of the large chelate ring size on metal ion stability and selectivity is of interest. No structural chemistry has been reported for either the $Ln - tams$ or $Ln - taps$ systems. However, as demonstrated with the group 13 metals, variations in the number of potential donor atoms, the number of chelate rings formed upon coordination, and the size of the chelate rings formed (5- or 6-membered rings) can have a profound effect upon metal ion selectivity and coordination geometry (see Figure 13). Instead this change in backbone results in a dramatic change in binding modality in that H_6tams and H_6taps react with $Ln(III)$ ions in the presence of base to form encapsulated complexes wherein all 6 donor atoms of the ligand (*i.e.* N_3O_3 , coordination) coordinate to the lanthanide ion. This change in coordination mode

relative to H_6trns (capped, bicapped) also produces a lower selectivity for heavy lanthanide chelation.

Changing the phenolic oxygen donor atoms of H_6trns to phosphinic acids, H_3ppma (see Figure 12), results in bicapped binding for the group 13 metals (see Figure 13). The first stepwise equilibrium constant K_1 (formation of the monocapped species) is less than that of the second K_2 (formation of the bicapped species). This behavior was also noted in the lanthanide H_3trns^3 system. It was found that the difference between K_1 and K_2 increased as the metal ion size increased. In light of this size effect, this phenomenon was explored further by using larger metal ions, i.e. the lanthanides. The results of the reactions of $Ln(III)$ with H_3ppma , where bicapped species are formed, are demonstrated. The anomalous equilibrium constant behavior was also observed and is discussed in relation to the similar trend observed for H_6trns , whereby the anomaly can be described in terms of hydrophobic effects.

Examples

Materials. Sodium deuterioxide ($NaOD$, 40%), deuterium chloride (DCl , 12M) and the lanthanide atomic absorption standards were obtained from Aldrich. Hydrated lanthanide nitrates and chlorides were obtained from Alfa. Deuterium oxide (D_2O) and methanol- d_4 (CD_3OD) and $DMSO-d_6$ were purchased from Cambridge Isotope Laboratories. All were used without further purification. Tris(4-phenylphosphinato-3-methyl-3-azabutyl)amine trihydrochloride monohydrate ($H_3ppma \cdot 3HCl \cdot H_2O$),⁸ 1,1,1-tris(((2-hydroxy-5-sulfobenzyl)amino)methyl)ethane dihemihydrate ($H_6tams \cdot 2.5H_2O$)⁶ and 1,2,3-tris((2-hydroxy-5-sulfobenzyl)amino)propane dihemihydrate ($H_6taps \cdot 2.5H_2O$)⁶ were prepared.

Instruments. 1H NMR spectra (200 and 300 MHz) were referenced to DSS or TMS and recorded on Bruker AC-200E and Varian XL 300 spectrometers. ^{13}C NMR (75.5 MHz, referenced to DSS or TMS), ^{31}P NMR (121.0 MHz,

referenced to H_2O), and ^{139}La NMR (42.4 MHz, referenced to 0.1 M $\text{La}(\text{ClO}_4)_3$ in 1 M HClO_4) spectra were recorded on the latter instrument. Mass spectra were obtained on a Kratos Concept II H32Q (Cs^+ , LSIMS) instrument with thioglycerol or 3-nitrobenzyl alcohol as the matrix. Infrared spectra were obtained as KBr disks in the range 4000 - 400 cm^{-1} on a Galaxy Series 5000 FTIR spectrometer. Analyses for C, H, and N were performed.

Synthesis of Lanthanide- H_3ppma Complexes. The preparation of the lutetium complex (as the trihydrate) is representative for the lanthanides Er - Lu and the preparation of the terbium complex (as the pentahydrate) is representative for the lanthanides Sm - Ho, Yb, Lu (in the case of Sm, Eu and Ho the metal chloride was used). All the complexes prepared and their elemental analyses, mass spectral, infrared and NMR data are listed in Tables 1 - 4.

[Lu(H_3ppma) $_2$][NO $_3$] $_3$ ·3 H_2O . The pH of an aqueous solution (4 mL) of H_3ppma ·3 HCl · H_2O (0.200 g, 0.257 mmol) and $\text{Lu}(\text{NO}_3)_3$ ·6 H_2O (0.060 g, 0.128 mmol) was raised to 2.0 using 3M NaOH. Colorless prisms deposited after 2 hours; these prisms were filtered and dried under vacuum to yield 0.145 g (66.0%). Yield for Yb 78.4%, Tm 50.2%, Er 53.0%.

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[Tb(H_3ppma) $_2$][NO $_3$] $_5$ ·5 H_2O . An aqueous solution (0.7 mL) of H_3ppma ·3 HCl · H_2O (0.100 g, 0.128 mmol) was added to $\text{Tb}(\text{NO}_3)_3$ ·5 H_2O (0.057 g, 0.128 mmol) in 0.7 mL of H_2O . Colorless hexagonal crystals deposited after 24 hours; these were filtered and dried under vacuum to yield 0.064 g (57.6%).

Yields for Lu 70.5%, Yb 73.4%, Ho 43.2%, Dy 50.1%, Gd 63.1%, Eu 40.3%, Sm 47.9%.

NMR Measurements. The variable pH ^1H NMR spectra of the H_6tams and H_6taps complexes were run in D_2O with the pD values being measured by a Fisher Accumet 950 pH meter employing an Accumet Ag/AgCl combination

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microelectrode. The pD values were converted to pH by adding 0.40 to the observed reading. The ^{17}O NMR experiments with Dy(III) were recorded at 21°C, with a spectral window of 1000 Hz, a 90° pulse width of 18 ms, and an acquisition time of 0.256 s; this gave 512 data points. Two thousand transients were collected per spectrum. The ^{17}O linewidths for H_2O were about 60 Hz. Concentrations employed ranged from 1 to 40 mM. The dysprosium induced shifts (DIS) were obtained from the observed shift by making a correction for the bulk magnetic susceptibility of the solution. Stock solutions were prepared from metal nitrates in D_2O (H_2O) and the metal-ligand solutions were prepared by pipetting required amounts of stock solution and adjusting the pH with acid or base. In the equilibrium measurements, the ionic strength was controlled by addition of NaCl.

For the Ln - H_3ppma (Ln = Yb, Lu) equilibrium constant studies using $^{31}\text{P}\{\text{H}\}$ NMR, conditions as described in the publication, J. Am. Chem. Soc. 1996, 118, 10446-10456, were used. Metal ion stock solutions (50 mM) were prepared from the hydrates of $\text{Lu}(\text{NO}_3)_3$ and $\text{Yb}(\text{NO}_3)_3$. All solutions contained a fixed amount of M^{3+} (25 mM) with the ligand concentration varied ($R = [\text{L}]_{\text{T}}/[\text{M}]_{\text{T}}$) as $0.25 < R < 4$. Solutions were made up to a volume of 0.8 mL and the pH was adjusted to 1.5. The solutions were allowed to equilibrate for 48 hours prior to the spectra being collected. The respective peak integrals enabled a quantitative measurement (long delay times of 1.6 s were employed) of free ligand ($[\text{L}]$). The knowledge of $[\text{L}]$ allowed \bar{n} , the ratio of bound ligand to total metal to be calculated ($\bar{n} = ([\text{L}]_{\text{T}} - [\text{L}])/[\text{M}]_{\text{T}}$). A plot of \bar{n} vs. $[\text{L}]$ resulted in a curve from which the variables β_1 and β_2 could be calculated using computer curve fitting software.

Potentiometric Equilibrium Measurements. The procedure was the same as detailed in J. Am. Chem. Soc. 1995, 117, 11230. The measurements were made at $25.0 \pm 0.1^\circ$, $m = 0.16 \text{ M NaCl}$. The pK_a s of the ligands were checked whenever a different synthetic batch of ligand was used, and fresh ligand solutions were always employed (For H_6taps : $\text{pK}_{a1} = 1.7$, $\text{pK}_{a2} = 6.54$, $\text{pK}_{a3} =$

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7.78, $pK_{a4} = 8.73$, $pK_{a5} = 9.77$, $pK_{a6} = 11.24$ and for H_6tams : $pK_{a1} = 2.92$, $pK_{a2} = 6.56$, $pK_{a3} = 7.95$, $pK_{a4} = 8.91$, $pK_{a5} = 9.81$, $pK_{a6} = 11.19$).⁶ The lanthanide solutions were prepared by dilution of the appropriate atomic absorption standards. Since the lanthanides do not hydrolyze below pH 6, the excess acid in the solutions could be obtained by titrating with standard NaOH and analyzing for the strong acid by the method of Gran.

The ratio of ligand to metal used was $1:2 < L:M < 4:1$. Concentrations were in the range 0.5 - 2.5 mM. A minimum of five titrations were performed for each metal. The metal - H_6taps and metal - H_6tams solutions were titrated to just beyond six equivalents NaOH / H_{6taps} (H_6tams), because of slow hydrolysis beyond this point. Although complexation was rapid (1-3 min per point to give a stable pH reading), care was taken to ensure that no trace hydrolysis or precipitation was occurring by monitoring up to 30 minutes for pH drift. The protonation constants for the lanthanide-ligand stability constants were determined by using the program BEST. H_6tams and H_6taps , both reacted with Ln(III) to coordinate as hexadentate ligands, liberating six equivalents of acid per ligand. Typically 100 data points were collected with about 80-90% of the points being in the buffer region of metal-ligand complexation and the remaining points in the strong acid region being used as a check of excess acid concentration.

X-ray Crystallographic Analyses of $[C_{60}H_{20}LuN_3O_{12}](NO_3)_3 \cdot 3H_2O$.

Selected crystallographic data appear in Table 5. The final unit-cell parameters were obtained by least-squares on the setting angles for 25 reflections with $2\theta = 55.7-68.7^\circ$. The intensities of three standard reflections, measured every 200 reflections throughout the data collection, decayed linearly by 2.7%. The data were processed and corrected for Lorentz and polarization effects, decay, and absorption (empirical, based on azimuthal scans).

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The structure of $[\text{C}_{60}\text{H}_{90}\text{LuN}_4\text{O}_{12}](\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$ was solved by the Patterson method. The structure analysis was initiated in the centrosymmetric space group $R\bar{c}$ on the basis of the E -statistics, this choice being confirmed by subsequent calculations. The nitrate anions and water molecules were modeled as (1:1) disordered about a point of S_6 symmetry. Because of thermal motion and near overlap of disordered components, the nitrate groups deviate from ideal geometry. Refinement of the structure in the noncentrosymmetric space group $R3c$ failed to resolve the disorder. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were fixed in calculated positions (N-H = 0.91 Å, C-H = 0.98 Å, $B_{\text{H}} = 1.2 B_{\text{bonded atom}}$). A correction for secondary extinction (Zacharaisen type) was applied, the final value of the extinction coefficient being $1.73(3) \times 10^{-7}$. Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from the *International Tables for X-Ray Crystallography*. Selected bond lengths and bond angles appear in Table 6. Complete tables of crystallographic data, final atomic coordinates and equivalent isotropic thermal parameters, anisotropic thermal parameters, bond lengths, bond angles, torsion angles, intermolecular contacts, and least-squares planes are included as Supporting Information.

Results

$[\text{Ln}(\text{H}_3\text{ppma})_2]^{3+}$ (Ln = Lu - Sm). The synthesis of the bisligand complexes as hydrated salts was achieved by mixing stoichiometric (L:M = 2:1) amounts of aqueous solutions of metal nitrate or chloride and H_3ppma (with Er - Lu the pH was raised to 1.5). Precipitation of the resulting complexes occurred within a few hours to days, depending on the metal ion. The lanthanide complexes fall into two categories: the complexes of the smaller, heavier lanthanides (Er - Lu) were prepared in the same manner as their group 13 metal analogs yielding cubic crystals, which analyzed as trihydrates. The complexes of the lighter lanthanides (Sm - Ho, and Yb, Lu for comparison) were prepared in a similar manner, however, no pH adjustment was made. Hexagonal plates were obtained;

these analyzed as pentahydrates (and which were used, two additional hydrochlorides were found). It is expected that this additional hydration is due to a different crystal lattice formed at lower pH, however the thin plates proved unsuitable for X-ray analysis. The IR spectra of the Er - Lu complexes resembled their group 13 analogs, with one of the three P-O stretches shifted to lower wavenumber as the metal ion increased in size, a trend which persisted through the lanthanide series from samarium to lutetium ($V_{PO} = 1154 - 1165 \text{ cm}^{-1}$). The P-O stretch at the highest wavenumber for the trihydrates, when $Ln = \text{Er} - \text{Lu}$ ($V_{PO} = 1194 - 1190 \text{ cm}^{-1}$) changed for the pentahydrates of the earlier lanthanides $Ln = \text{Sm} - \text{Ho}$ and Yb, Lu ($V_{PO} = 1183 - 1180 \text{ cm}^{-1}$) likely due to a slight change in structure ($3\text{H}_2\text{O}$ vs. $5\text{H}_2\text{O}$). It is unclear whether this is attributable to differences in hydrogen bonding or to a different coordination number; however, a large shift in the V_{NH} stretch ($\Delta V_{NH} = 300 \text{ cm}^{-1}$) along with a change of V_{PO} indicated a change in hydrogen bonding strength. The LSIMS (+) mass spectra showed molecular ions $[\text{ML}_2\text{-}2\text{H}]^+$ and $[\text{ML}_2\text{-H}]^{2+}$ at the appropriate m/z value for the bicapped species, and ions for the monoligand species $[\text{ML} - 2\text{H}]^+$ and for the free ligand $[\text{L} + \text{H}]^+$ at $m/z = 651$.

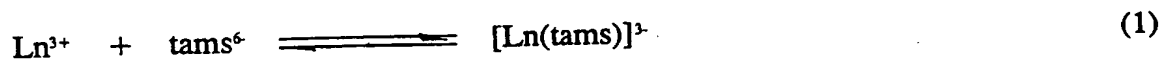
X-ray Crystal Structure of $[\text{Lu}(\text{H}_3\text{ppma})_2][\text{NO}_3]_3 \cdot 3\text{H}_2\text{O}$. Colorless

prisms crystallized in the space group $R\bar{3}c$. ORTEP representations of the $[\text{Lu}(\text{H}_3\text{ppma})_2]^{3+}$ cation is shown in Figures 1 and 2, and selected bond distances and angles are listed in Table 6. The structure is of a bicapped ML_2 , similar to that observed for the bisligand tren-based aminephenolate-lanthanide complexes and is isostructural and isomorphous with the indium structure previously reported. The complex cation has exact S_6 symmetry. The O-Lu-O trans angle is crystallographically imposed at 180.0° , and the cis O-Lu-O angles are $88.72(6)$ and $91.28(6)^\circ$, resulting in near perfect octahedral geometry, expected because the ionic radius of Lu^{3+} (0.861 \AA) is similar to that of In^{3+} (0.800 \AA) i.e. the ideal size to accommodate two ligands in a bicapped manner. The Lu-O distances of $2.190(2) \text{ \AA}$ are in the expected range, although few six-coordinate lutetium structures have been reported. This distance is only slightly longer than the In-O

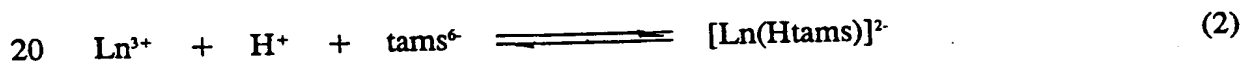
distance (2.117(3) Å) in the indium structure, again reflecting the similar size of the ions. On coordination to the metal ion, the phosphorus atoms are rendered chiral, with one half of the bicapped structure possessing all R chirality and one half all S, i.e. the cation is the RRRSSS diastereomer. This opposing RRRSSS
 5 chirality generates the six fold symmetry and is indeed necessary to accommodate the six bulky phenyl rings because, once the phosphinates coordinate, the phenyls completely engulf the coordination sphere. Highly ordered intramolecular hydrogen bonding is observed from the protonated nitrogen N(2) to the phosphinate oxygen O(2) on an adjacent arm, where H...O = 1.87 Å (N...O = 2.684(3) Å)
 10 and N—H...O = 147°.

Formation Constants Figure 3 shows experimental titration curves for the lanthanides with H₆tams (top) and H₆taps (bottom) at a ratio of 2 mM Ln(III) : 2 mM ligand. The following equilibrium conventions apply to these two systems,

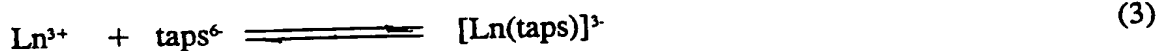
15 i.e.



$$K_{\text{Ln}(\text{tams})} = [[\text{Ln}(\text{tams})]^{3-}]/[\text{Ln}^{3+}][\text{tams}^{6-}]$$

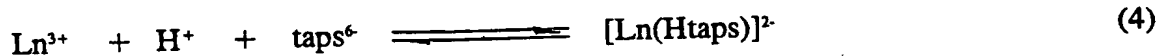


$$K_{\text{Ln}(\text{Htams})} = [[\text{Ln}(\text{Htams})]^{2-}]/[\text{Ln}^{3+}][\text{H}^+][\text{tams}^{6-}]$$



$$K_{\text{Ln}(\text{taps})} = [[\text{Ln}(\text{taps})]^{3-}]/[\text{Ln}^{3+}][\text{taps}^{6-}]$$

25



$$K_{\text{Ln}(\text{Htaps})} = [[\text{Ln}(\text{Htaps})]^{2-}]/[\text{Ln}^{3+}][\text{H}^+][\text{taps}^{6-}]$$

ligands are coordinating in a hexadentate fashion and the atoms; this is verified (and further emphasized) in the \bar{n} plots (Figure 4) where the curves rise to $\bar{n} = 1$ and then plateau, even in the experiments with excess ligand.

- 5 Analysis of the potentiometric data gave the stability constants listed in Table 7. It was necessary to include monoprotonated complexes in the model to improve the fit of the data, although these only form to a small extent (maximum ~ 25% of total Ln(III)). Both tams^6 and taps^6 are selective for the heavier lanthanides, but much less so than is H_3trns^3 .

10

- Because of the very low pK_a 's for H_3ppma , formation constants for the ytterbium and lutetium complexes of H_3ppma were determined by a ^{31}P NMR approach highlighted previously. ^{31}P NMR spectra were recorded for a series of solutions ($R = [\text{L}]_T/[\text{M}]_T$, $\text{L} = \text{H}_3\text{ppma}$, $\text{M} = \text{Yb, Lu}$) in the range $0.24 < R <$
 15 3.80 (where $[\text{Lu}] = [\text{Yb}] = 25\text{mM}$). A representative sample for the Yb study is shown in Figure 5. The resonance for free H_3ppma is clearly distinct from those for the metal complexes (ML and ML_2). Two resonances for both RRRSSS and RRSSSR diastereomers were noted, as was seen in the group 13 study. It is much more difficult to assign these resonances as specific 1:1 and 2:1 species (c.f. the
 20 case of the group 13 metals where the additional tool of the metal NMR was invaluable), however the concentration of free ligand $[\text{L}]$ is readily obtained from the integrals. From this value, \bar{n} can be calculated for each experiment (see experimental and ref. 8). Assuming the formation of the 1:1 and 2:1 complex (equations 5 and 6) where $\text{M} = \text{Yb, Lu}$ and $\text{L} = \text{H}_3\text{ppma}$, and using mass balance equations,
 25 \bar{n} (the ratio of bound ligand to total metal) can be expressed as equation 7 in terms of the formation constants β_1 , β_2 and free ligand $[\text{L}]$.



$$30 \quad \bar{n} = (\beta_1[\text{L}] + 2\beta_2[\text{L}]^2) / (1 + \beta_1[\text{L}] + \beta_2[\text{L}]^2) \quad (7)$$

From a plot \bar{n} vs. $[L]$ values of the formation constants are obtained for Lu are $\log \beta_1 = 1.79$ (7), $\log \beta_2 = 4.40$ (2) and for Yb $\log \beta_1 = 2.25$ (7), $\log \beta_2 = 4.42$ (5). A plot of \bar{n} vs. $\log [L]$ for Lu and Yb (also included is the data for Al, Ga and In) is shown in Figure 6. The curves rise to $\bar{n} = 2$ and then plateau, indicating formation of a 2:1 species.

Multinuclear NMR (^1H , ^{13}C , ^{31}P , ^{139}La). Solution NMR studies on the Ln(III) - H_6tams and Ln (III) - H_6taps systems were unrevealing. The ^1H NMR and ^{13}C NMR spectra of $[\text{Lu}(\text{taps})]^{3+}$ in D_2O at pD 9 showed a series of broad overlapping resonances characteristic of fluxional behavior. The ^1H NMR spectra of $[\text{Lu}(\text{tams})]^{3+}$, $[\text{La}(\text{tams})]^{3+}$, and $[\text{La}(\text{taps})]^{3+}$ were similar to those of the free ligand suggesting fast exchange. A ^{139}La NMR study of 30 mM La(III) : 30 mM H_6taps as a function of pH showed only one resonance at 0 ppm, the chemical shift of $\text{La}_{(\text{aq})}^{3+}$. The linewidth of this resonance increased with pH suggesting that $[\text{La}(\text{taps})]^{3+}$ is in exchange with $\text{La}_{(\text{aq})}^{3+}$.

The ^1H NMR spectra of the $[\text{Ln}(\text{H}_3\text{ppma})_2]^{3+}$ complexes in CD_3OD where Ln = Er - Lu, all exhibit ten resonances, corresponding to the ten hydrogens labeled in Figure 7, the spectrum of the thulium complex. The observance of only 10 resonances clearly indicates the persistence of the S_6 symmetry in solution for all these H_3ppma complexes. The spectrum of the diamagnetic lutetium complex greatly resembles those obtained for the same structure with the group 13 metals, and is most similar to that of the indium complex, consistent with the similar ionic radii of the two metals. The resonances can be readily assigned from their coupling patterns (Lu), from their 2D ^1H - ^1H COSY spectra, and from comparison with the group 13 metal complexes of H_3ppma . With the paramagnetic lanthanide (Er - Yb) complexes, dramatic chemical shifts are noted, with well resolved and narrow resonances. The ^{31}P NMR spectra of these four late lanthanide complexes also exhibit the S_6 symmetry in solution, showing a single narrow resonance for all six equivalent phosphorus atoms.

- change in the respective $^1\text{H}/^{31}\text{P}$ NMR spectra is noted. The ^{31}P NMR spectra no longer indicate a single species in solution, (four resonances are usually observed) resulting in a proliferation of resonances in the corresponding ^1H NMR spectra.
- 5 The chemical shifts of the ^{31}P NMR resonances suggest that only complexes are present, i.e. no resonance for free H_3ppma is evident, and thus one must assume that the solvent CD_3OD is interacting with the bicapped complex forcing changes in geometry and/or stoichiometry. Even from these complex spectra, the 10 resonances corresponding to the RRRSSS diastereomer can usually be picked out
- 10 when the lanthanide in question causes sufficient chemical shift separation (Tb - Ho). If a different solvent is used, i.e. $\text{DMSO}-d_6$, a dramatic simplification of the spectrum is observed. Ten resonances (broader than in CD_3OD) of the RRRSSS diastereomer are observed in the ^1H NMR spectrum, along with the spectrum of H_3ppma . This is reciprocated in the ^{31}P NMR spectrum where two resonances are
- 15 seen, one of which is present in the CD_3OD spectrum and a new one of free H_3ppma . Interestingly, if the Yb and Lu complexes are prepared in the same manner as Sm - Ho, i.e. no pH adjustment, as hexagonal crystals (analyzing as the pentahydrate), their respective NMR spectra are the same as those obtained by raising the pH (as the trihydrate) i.e. no decomposition or rearrangement is noted,
- 20 which suggests the lanthanide is sufficiently small and/or tightly bound to prevent solvent interaction with metal ion.

- The shift, Δ , induced at a nucleus of a ligand binding to a Ln(III) cation can be expressed as the sum of the diamagnetic shift (Δ_d), the contact shift (Δ_c),
- 25 the pseudocontact shift (Δ_p), and the shift due to the bulk magnetic susceptibility (Δ_e), equation (8).

$$\Delta = \Delta_d + \Delta_c + \Delta_p + \Delta_e \quad (8)$$

$$30 \quad \Delta_e = 4\pi C(\mu_{\text{eff}}/2.84)^2/3T \quad (9)$$

The diamagnetic shift, which is usually relatively small, can be obtained from the shift of $[\text{Lu}(\text{H}_3\text{ppma})_2]^{3+}$. Since the magnetic moments of the Ln(III) ions are relatively constant, the bulk magnetic susceptibility shift can be estimated from equation (9) which applies to a superconducting solenoid, where C is the concentration (mM) of Ln(III), m_{eff} is the effective magnetic moment for Ln(III), and T is the temperature (K). Calculated m_{eff} values were taken from Figgis, *Introduction to Ligand Fields*. The contact and pseudocontact shifts can be expressed by equation (10)¹⁷ where D_c and D_p are each expressed as the product of two terms.

$$\Delta' = \Delta - (\Delta_c + \Delta) = \Delta_c + \Delta_p = \langle S_z \rangle F + C^p G \quad (10)$$

The first term ($\langle S_z \rangle$ or C^p) is characteristic of the lanthanide, but independent of the ligand, while the second term (F or G) is characteristic of the ligand in question, but independent of the Ln(III) cation. Values for the lanthanide dependent contact term, $\langle S_z \rangle$, and pseudocontact term, C^p , have been calculated. Equation (10) can be separated into two linear forms, equations (11) and (12). Although, both (11) and (12) are mathematically identical, Reilley et al. have advocated the use of equation (11) when $F \gg G$ (and equation (12) when $G \gg F$) since the dependence on theoretical C^p (or $\langle S_z \rangle$) will be minimized by a small intercept.

$$\Delta'/C^p = F(\langle S_z \rangle/C^p) + G \quad (11)$$

$$\Delta'/\langle S_z \rangle = G(C^p/\langle S_z \rangle) + F \quad (12)$$

Figure 8 shows a plot of D'/C^p vs. $\langle S_z \rangle/C^p$ for the ^1H NMR spectra (top) and for the ^{31}P NMR spectra (bottom). For an isostructural series a linear relationship is expected, whereby the parameters F and G may be obtained from slopes and intercepts of plots derived from equation 11 or 12. This is clearly not

observed in the
Ho would be expected as analysis reveals additional water in the solid state,
however a correlation for Er - Yb would be certainly assumed as all evidence
points to an "isostructural miniseries", it is evident from these plots that there
5 must be some change in ligand orientation.

¹⁷O NMR: The natural abundance ¹⁷O NMR of water in the presence
of a lanthanide ion and ligand gives a qualitative picture of complexation. Peters
and coworkers have exploited the dysprosium induced shift of water (Dy.I.S.) to
10 estimate quantitatively the number of bound water molecules associated with
various lanthanide complexes. The Dy.I.S. of water was measured at varying
dysprosium concentrations. The plot of Dy.I.S. versus [Dy(III)] was linear with a
slope of -358 ppm/M. It had been previously established that the contact contribu-
tion in a paramagnetic Ln(III)-induced shift of a Ln(III)-bound ¹⁷O nucleus is
15 almost independent of the nature of the probed O-containing ligand in question and
of other co-ligands coordinated to the lanthanide. Since the ¹⁷O shift is predomi-
nantly contact in nature, the slope of a plot of Dy.I.S versus [Dy(III)] should be
proportional to the number of bound water molecules associated with the complex.
If the hydration number of Dy(III) is taken to be eight, then a slope of -358/8 =
20 -45 would be indicative of one bound water and each multiple of 45 corresponds
to one water. Figure 9 shows the Dy.I.S. versus [Dy(III)] for Dy_(aq)³⁺, [Dy(tams)]³⁺
and [Dy(taps)]³⁺ ([Dy(H₃trns)₂]³⁺ is shown for comparison). The slope of -358
ppm/M for Dy_(aq)³⁺ is in excellent agreement with that obtained by Alpoim et al.
(-357 ppm/M) and by Reuben and Fiat (-360 ppm/M). The error bars show the
25 linewidths at half height (60 Hz); however, the precision was ± 5 Hz. All three
plots were linear with correlation coefficients of greater than 0.999. The slopes
for [Dy(tams)]³⁺ and [Dy(taps)]³⁺ were -128 ppm/M (2.8 H₂O) and -123 ppm/M
(2.7 H₂O), respectively. Ratios of tams⁶⁻ : Dy(III) and taps⁶⁻ : Dy(III) as high as 8
showed a limiting stoichiometry of 1 tams⁶⁻ : 1 Dy(III) and 1 taps⁶⁻ : 1 Dy(III). A
30 study of the hydration of the Dy - H₃ppma system was attempted; however, even

at large excesses of ligand, multiple species were present.

Discussion

5 We have discovered that H_3ppma forms highly (S_6) symmetrical bis(ligand) complexes with the lanthanides Sm - Lu, analogous to those formed with the group 13 metals. Indeed, the X-ray structure of the lutetium complex is isostructural and isomorphous with that of the indium structure. The high symmetry is preserved in solution, indicated in the 1H and ^{31}P NMR spectra. Such
10 evidence indicates an isostructural series of compounds from and Sm - Lu. In light of this, it was expected that the paramagnetic shifts of the 1H and ^{31}P resonances could be resolved into contact and pseudocontact components, once corrected for diamagnetic and bulk magnetic susceptibility contributions. However, a linear relationship for Δ'/C^D vs. $\langle S_z \rangle / C^D$ (or $\Delta' / \langle S_z \rangle$ vs. $C^D / \langle S_z \rangle$) was not
15 forthcoming. Such a failure to correlate is usually a result of changing coordination geometry or number. In the case of H_3ppma all evidence (NMR, mass spectral, IR and elemental analyses) points towards an isostructural series, especially for Er - Lu. It is evident that subtle changes in ligand orientation about the paramagnetic lanthanide as the ionic radius increases causes sufficiently large
20 changes in chemical shift, to prevent a linear correlation, i.e. the interlocking phenyl groups must move further apart to some extent to accommodate the larger metal ion, even if the change in ionic radius is only small. The opposite of this, i.e. the compression of the phenyl rings was the rational for the greater stability of the indium complex with respect to the gallium and aluminum. Indeed the
25 chemical shift of the hydrogens ortho to phosphorus in the phenyl rings (H_F) show a progressive shift to lower frequency Al-Ga-In-Lu. For these small changes in geometry to cause such a large effect suggests a large pseudocontact contribution to the chemical shift, as it is this contribution which contains structural information. It is stated that if geometric information for a substrate is to be obtained, the
30 complex must have axial symmetry (at least three fold), it would be expected that the S_6 symmetry here would be more than sufficient.

The bis(ligand) complexes obtained for H_3ppma are similar to those obtained⁷ with H_3trns^3 . In this latter case the oxygen donor group is phenolato as opposed to phosphinato. Similar anomalous behavior was observed in the formation constants of the mono vs. bisligand complexes, i.e. K_2 was found to be greater than K_1 , an unusual occurrence, demanding explanation. In the H_3trns^3 : Ln(III) system, it was thought likely that this unusual phenomenon was predominantly an entropic effect; the nature of the H_3trns^3 : Ln(III) system suggests that there should be no favorable enthalpy associated with K_2 (relative to K_1) based on electrostatic arguments, and a lowering of coordination number. As the first equivalent of H_3trns^3 displaced 3 waters, while the second equivalent displaced 5 waters, this second equilibrium increased the translational entropy of the system more than the first, and was thus manifested in the larger value of K_2 . This argument was supported by calorimetric measurements, which showed $\Delta S_2 > \Delta S_1$ for each Ln(III) studied.

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An alternative argument can be proposed for the anomalous $K_2 > K_1$ effect based upon the *hydrophobic effect*. Consider the solvation of a gaseous hydrocarbon in water at 25 °C. This process involves a small negative enthalpy of solvation, but a larger negative entropy of solvation; it is thermodynamically disfavored because of entropy. The aggregation of apolar solutes is then driven by entropy such that the water molecules avoid entropically unfavorable interactions with the apolar solute molecules. H_3trns^3 and H_3ppma can be thought of as amphiphilic species with charged polar regions and three apolar aryl rings. Describing the two equilibria, K_1 and K_2 , pictorially as in Figure 10 for H_3ppma (the charges differ for H_3trns^3) leads to a hydrophobic interpretation of the two complexation reactions. The areas shaded in grey represent the hydrophobic aryl portions of the molecules.

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In the first step (K_1) one ion with a hydrophobic region combines with a lanthanide ion to give a molecule with a hydrophobic region. The second step (K_2) is the combination of a monoligand species with a second ligand, each with a

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hydrophobic region, combining to give an ion with only one hydrophobic region. This minimization of solvent (H_2O) accessible hydrophobic regions, or "a tightening of the hydrophobic belt", should be reflected in a more positive entropy for K_2 relative to K_1 , as was observed for H_3trns^3 . Both steps are also enthalpically favored by the formation of $Ln - O$ (phenolate) bonds. This hydrophobic interpretation of the complexation can also be invoked to explain the similar anomalous behavior on the equilibria of the ligand H_3ppma when complexed to the group 13 metals. Topologically the ligand is almost identical to that of $trns^6$, having a tripodal tren-based structure bearing pendant donors incorporating a hydrophobic aryl region. H_3ppma reacts with the group 13 metals and with the lanthanides to form capped and bicapped complexes by coordinating to the metal through the phosphinato oxygen atoms. The second stepwise equilibrium constant is markedly greater than the first in the case of the group 13 metals and less so, but still significantly large, in the case of the lanthanides.

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Since the aquo ions of $Al(III)$, $Ga(III)$, and $In(III)$ are known to be six coordinate and the bicapped complexes contain octahedral ions, the argument presented previously for $trns^6$ i.e. for an inner sphere desolvation and lowering of coordination number does not apply. However this anomalous behavior can be rationalized by the hydrophobic effect as shown in Figure 10. In the case of the lanthanides, a reduction of solvation may play a part, but again it is likely that this hydrophobic explanation is applicable. The difference in K_2 vs. K_1 is not as startling as for the group 13 metals even though the formation of a six-coordinate lanthanide complex would be expected to exhibit an even greater entropic effect on moving from a monocapped species with the expulsion of 5 bound waters. The major difference in this case is the increase in size of the coordinated metal ion. H_3ppma showed an increased affinity for the larger metals in group 13, where $\log K$ for $In > Ga > Al$, with an increase by an order of magnitude in each case. The preference for indium was attributed to the ionic radii of the metals, indium being of ideal size to accommodate the bulky phenyl groups on coordination. The determination of the formation constants of the group 13 metals was carried out

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via a combined ^{31}P - $^{27}\text{Al}/^{71}\text{Ga}$ NMR spectroscopic method, as the use of more conventional methods (potentiometry) was obviated by the very low pK_a 's of the phosphinic hydroxyls and lack of chromophores (UV/Vis). In the case of the lanthanide complexes, the study was restricted to diamagnetic Lu(III) and paramagnetic Yb(III) . Attempts with any earlier lanthanides were thwarted by increasing line widths and overlapping of resonances. Even so, a trend is noted, which can be readily explained by considering the "tightening of hydrophobic belt". Indium, it would appear, is the ideal size to accommodate the six phenyl rings in a strain-free manner, whilst still excluding solvent from the coordination sphere. The lanthanides show an marked increase in K_1 with respect to the group 13 metals, which can be attributed to their increased ionic radii. The larger the metal ion, the further apart the two ligands become, thus allowing more solvent to be in contact with the hydrophobic areas of the complex (Figure 10), hence the hydrophobic belt is somewhat loosened. This is reflected in the decrease in K_1 relative to K_2 as we move from Yb(III) to Lu(III) , indeed it appears that on moving to the larger lanthanides (Ho - Sm) the phenyls will be sufficiently separated to perhaps allow water coordination, or at least interference of solvent causing a break up of the complexes, as was highlighted by the ^1H and ^{31}P NMR spectra of these complexes in CD_3OD . This may also be the cause of the non-correlation of the lanthanide induced shift NMR data.

When H_6trns^3 binds to a lanthanide(III) in a tridentate fashion, there should be no chelate effect - three sixteen membered chelate rings are formed. Given the relatively high stability found for these capped 16-membered ring complexes, there must be an effect which predisposes the ligand to a binding posture. The flexibility imparted by a loose H-bond network coupled with the large chelate ring size results in a tridentate ligand which should have little or no strain energy created in accommodating different Ln(III) ions; thus the increase in stability is purely electrostatic and increases with the inverse ionic radius of the lanthanide considered. In order to further explore the effect of large chelate ring size on Ln(III) selectivity, solution studies with H_6tams and H_6taps were under-

taken. If these two ligands reacted in the same manner as H_6trns , then lanthanide complexes containing 14-membered and 13-membered chelate rings would be formed. Instead of coordinating solely through the phenolato donor atoms, $tams^6$ and $taps^6$ coordinated through the three amino nitrogen and three phenolato oxygen donor atoms. A major difference between H_6trns and H_6tams or H_6taps is the microscopic order of deprotonation. It had been shown that the first three deprotonation events of H_6trns occur at phenolic sites,⁷ whereas H_6tams and H_6taps are firstly deprotonated at an ammonium site, followed by three phenol sites, and then the remaining two ammonium groups. The first deprotonation of H_6tams and H_6taps occurs at a pH much lower than that at which $Ln(III)$ complexation occurs. Hence coordination to this amino group should be facile. Coordination to one amino group would necessarily bring the remaining ammonium groups closer to the metal ion to allow for proton displacement and lanthanide coordination to give the observed N_3O_3 ligand donor set. Variation of the donor group in changing from H_3trns^3 to H_3ppma , i.e. from phenolato to phosphinato showed no dramatic change in coordination as shown for $tams^6$ and $taps^6$. Indeed, none is expected as both ligands have nitrogen pK_a 's which are higher than the oxygen pK_a 's, the much lower phenolato and phosphinato pK_a 's dictate binding to the lanthanides exclusively through oxygen.

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The ^{17}O NMR study of both $[Dy(tams)]^3$ and $[Dy(taps)]^3$ indicated the presence of three inner sphere water molecules, implying a 9-coordinate $Dy(III)$ in each of the complexes. The change in coordination mode from H_3trns^3 to $tams^6$ and $taps^6$ has a profound effect on the metal ion selectivity. There is a large increase in stability upon going from $La(III)$ to $Nd(III)$ for all three ligands. However, on going from $Nd(III)$ to $Yb(III)$, H_3trns^3 exhibited a selectivity of about 2 log units per lanthanide studied. Here $tams^6$ exhibits lesser selectivity, about one log unit per lanthanide studied, whereas $taps^6$ has a much lower selectivity between $Gd(III)$ and $Yb(III)$. A better way of analyzing the data is to take into account the competition with hydrogen ion for the ligand by calculating pM values where $pM = -\log [M_{free}]$. This gives an impression of the relative sequestering

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ability of the ligands under a standard set of conditions. In Figure 11, pM values are calculated at pH 7.4 for a ligand to metal ratio of 10 : 1. The total concentration of Ln(III) is set at 1 mM; however since the stability constants for H_3trns^3 have an inverse square dependence on $[H_3trns^3]$, the pM values for $[Ln]_{\text{tot}} = 1\text{mM}$ have also been calculated to highlight this dilution effect. At millimolar concentrations and above, H_3trns^3 is the best ligand for complexing Nd(III) & Yb(III), and its sequestering ability increases with atomic number, Z. The much flatter curve for $taps^6$ indicates that it is less able to discriminate between the lanthanides.

10 The major structural difference between $taps^6$ and $tams^6$ is that $taps^6$ coordinates to a lanthanide forming four 6- and two 5-membered chelate rings, whereas $tams^6$ forms only 6-membered chelate rings upon coordination. An established tenet of coordination chemistry is that 5-membered chelate rings are more stable than 6-membered chelate rings and this difference in stability increases
15 with increasing metal ion size. This effect is manifested here where $[Ln(taps)]^{3-}$ complexes are 1 - 2 orders of magnitude more stable than the analogous $[Ln(tams)]^{3-}$ complexes.

Table 1. Elemental Analyses for $[\text{Ln}(\text{H}_3\text{ppma})_2](\text{X})_3 \cdot \text{YH}_2\text{O}$ ($\text{X} = \text{NO}_3, \text{Cl}$)

Formula	C		H		N	
	Calc	Found	Calc	Found	Calc	Found
$\text{C}_{60}\text{H}_{90}\text{LuN}_{11}\text{O}_{21}\text{P}_6 \cdot 3\text{H}_2\text{O}$	41.99	41.88	5.64	5.87	8.98	8.95
$\text{C}_{60}\text{H}_{90}\text{LuN}_{11}\text{O}_{21}\text{P}_6 \cdot 5\text{H}_2\text{O}$	41.13	41.26	5.75	5.65	8.79	8.55
$\text{C}_{60}\text{H}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6\text{Yb} \cdot 3\text{H}_2\text{O}$	42.04	42.34	5.64	5.60	8.99	8.91
$\text{C}_{60}\text{H}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6\text{Yb} \cdot 5\text{H}_2\text{O}$	41.17	41.19	5.76	5.62	8.80	8.68
$\text{C}_{60}\text{H}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6\text{Tm} \cdot 3\text{H}_2\text{O}$	42.14	42.24	5.66	5.61	9.01	8.79
$\text{C}_{60}\text{ErH}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6 \cdot 3\text{H}_2\text{O}$	42.18	41.88	5.66	5.87	9.02	8.95
$\text{C}_{60}\text{Cl}_3\text{H}_{90}\text{HoN}_8\text{O}_{12}\text{P}_6 \cdot 5\text{H}_2\text{O} \cdot 2\text{HCl}$	41.52	42.06	5.92	6.15	6.46	6.24
$\text{C}_{60}\text{DyH}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6 \cdot 5\text{H}_2\text{O}$	41.42	41.66	5.79	6.04	8.86	8.50
$\text{C}_{60}\text{H}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6\text{Tb} \cdot 5\text{H}_2\text{O}$	41.51	41.23	5.81	5.85	8.87	8.59
$\text{C}_{60}\text{GdH}_{90}\text{N}_{11}\text{O}_{21}\text{P}_6 \cdot 5\text{H}_2\text{O}$	41.55	41.61	5.81	5.63	8.88	8.53
$\text{C}_{60}\text{Cl}_3\text{EuH}_{90}\text{N}_8\text{O}_{12}\text{P}_6 \cdot 5\text{H}_2\text{O} \cdot 2\text{HCl}$	41.84	41.99	5.97	6.10	6.50	6.25
$\text{C}_{60}\text{Cl}_3\text{H}_{90}\text{N}_8\text{O}_{12}\text{P}_6\text{Sm} \cdot 5\text{H}_2\text{O} \cdot 2\text{HCl}$	41.87	42.13	5.97	6.14	6.51	6.38

Table 2. +LSIMS Mass Spectral Data for $[LnL_2]^{3+}$ ($L = H_3ppma$) Complexes

	$[ML_2-2H]^+$	$[ML-2H]^+$	$[ML_2-2H]^{2+}$
Lu*	1473	823	778
Yb*	1472	822	737
Tm	1467	817	734
Er	1466	816	733
Ho	1463	813	733
Dy	1462	812	731
Tb	1457	807	729
Gd	1456	806	728
Eu	1451	801	726
Sm	1450	800	726

* Identical spectrum obtained for trihydrate and pentahydrate

Table 3. IR data (cm⁻¹) for [Ln(H₃ppma)₂](X)₃·YH₂O (X = NO₃ or Cl⁺; Y = 3 or 5⁺) in cm⁻¹

	$\nu_{\text{OH/NH}}$	δ_{NH}	ν_{NO_3}	ν_{PO}	$\nu_{\text{PC/PPH}}$
Lu	3435, 2614	1642	1386	1194, 1136, 1065	745, 720, 579, 560
Lu ⁺	3431, 2426	1643	1385	1182, 1137, 1062	740, 719, 580, 553
Yb	3455, 2621	1644	1385	1193, 1135, 1062	743, 718, 579, 559
Yb ⁺	3429, 2441	1643	1384	1181, 1136, 1062	741, 720, 580, 553
Tm	3429, 2615	1644	1386	1194, 1135, 1063	745, 718, 580, 559
Er	2454, 2614	1641	1386	1192, 1134, 1061	743, 718, 578, 559
Ho ⁺⁺	3442, 2413	1644		1183, 1134, 1060	740, 719, 580, 553
Dy ⁺	3431, 2426	1644	1364	1181, 1134, 1058	741, 718, 580, 555
Tb ⁺	3429, 2410	1643	1386	1180, 1034, 1058	740, 718, 580, 553
Gd ⁺	3423, 2445	1644	1384	1180, 1035, 1057	740, 718, 580, 553
Eu ⁺⁺	3443, 2445	1643		1180, 1035, 1055	740, 718, 580, 553
Sm ⁺⁺	3418, 2460	1650		1180, 1133, 1054	741, 717, 580, 559

Table 4. ^1H and ^{31}P NMR Chemical Shifts^a for $[\text{Ln}(\text{H}_3\text{ppma})_2](\text{NO}_3) \cdot 5\text{H}_2\text{O}$ in CD_3OD ($\text{Ln} = \text{Er}$, Yb , Lu).

NMR spectra were referenced to TMS in CD_3OD (insert) and chemical shifts were corrected for bulk magnetic susceptibility $\Delta\chi$.

	$[\text{Tm}(\text{H}_3\text{ppma})_2]^{3+}$	$[\text{Er}(\text{H}_3\text{ppma})_2]^{3+}$	$[\text{Yb}(\text{H}_3\text{ppma})_2]^{3+}$	$[\text{Lu}(\text{H}_3\text{ppma})_2]^{3+}$
H_A	-17.04	-5.97	-0.27	3.24
$\text{H}_{\text{A}'}$	-13.06	-3.93	0.44	2.37
H_B	-22.92	-7.91	-0.63	4.74
$\text{H}_{\text{B}'}$	-26.94	-8.69	-0.76	3.00
H_C	-4.24	-0.02	1.88	3.03
H_D	-3.80	-1.93	2.14	2.30
$\text{H}_{\text{D}'}$	9.39	5.00	3.19	3.00
H_F	45.08	23.25	13.59	7.50
H_G	19.69	12.23	9.22	7.46
H_H	17.07	11.2	8.83	7.34
P	14.61	-6.86	34.41	15.29

a. For labelling see Figure 7.

Table 5. Selected Crystallographic Data for $\text{Lu}[(\text{H}_3\text{ppma})_2](\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$.

Compound	$[\text{C}_{60}\text{H}_{90}\text{LuN}_8\text{O}_{12}](\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$
Formula	$\text{C}_{60}\text{H}_{96}\text{LuN}_{11}\text{O}_{24}\text{P}_6$
fw	1716.29
Crystal system	Trigonal
Space group	$R\bar{3}c$
a , Å	19.060(1)
c , Å	36.395(3)
V , Å ³	11449(1)
Z	6
ρ_{calc} , g/cm ³	1.493
T , °C	21
Radiation	Cu
λ , Å	1.54178
μ , cm ⁻¹	43.66
Transmission factors	0.82-1.00
$R(F)$	0.024
$R_w(F)$	0.025

$$R = \sum \|F_o| - |F_c|\| / \sum |F_o|, R_w = (\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2)^{1/2}$$

Table 6. Selected Bond Lengths (Å) and Angles (deg)* for $[\text{Lu}(\text{H}_3\text{ppma})_2](\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$.

Lengths					
Atom	Atom	Distance	Atom	Atom	Distance
Lu(1)	O(1)	2.190(2)	P(1)	O(1)	1.492(2)
P(1)	O(2)	1.487(2)	P(1)	C(4)	1.826(3)
P(1)	C(5)	1.786(3)	N(1)	C(1)	1.471(3)
N(2)	C(2)	1.518(3)	N(2)	C(3)	1.498(4)
N(2)	C(4)	1.506(3)			

Angles							
Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
O(1)	Lu(1)	O(1) ^a	88.72(6)	O(1)	Lu(1)	O(1) ^b	180.0
O(1)	Lu(1)	O(1) ^c	91.28(6)	O(1)	P(1)	O(2)	119.1(1)
O(1)	P(1)	C(4)	103.5(1)	O(1)	P(1)	C(5)	108.41(10)
O(2)	P(1)	C(4)	109.8(1)	O(2)	P(1)	C(5)	111.3(1)
C(4)	P(1)	C(5)	103.5(1)	Lu(1)	O(1)	P(1)	145.2(1)
C(1)	N(1)	C(1) ^a	108.7(2)	C(2)	N(2)	C(3)	111.5(2)
C(2)	N(2)	C(4)	110.2(2)	C(3)	N(2)	C(4)	110.7(2)
N(1)	C(1)	C(2)	113.4(2)	N(2)	C(2)	C(1)	113.1(2)
P(1)	C(4)	N(2)	112.6(2)	P(1)	C(5)	C(6)	121.8(2)
P(1)	C(5)	C(10)	119.5(2)				

* (a) -y, x-y, z (b) -x, -y, 1-z (c) y, -x+y, 1-z.

Table 7. Log Formation Constants for Ln(III) with tams⁶⁻ and taps⁶⁻
at 25 °C, μ = 0.16 M NaCl.

Ln(III)	TAMS ⁶⁻		TAPS ⁶⁻	
	ML/M·L	HML/ML·H	ML/M·L	HML/ML·H
La	9.17 (1)	---	11.33 (3)	7.14 (2)
Nd	11.19 (6)	---	13.59 (3)	6.54 (3)
Gd	11.86 (9)	6.55 (9)	14.50 (1)	6.38 (4)
Ho	12.71 (10)	6.69 (4)	14.71 (4)	6.44 (9)
Yb	13.78 (1)	6.33 (3)	15.15 (3)	6.39 (4)

Conclusion

The complexation properties of an N_4O_3 tripodal aminomethylene phosphinato ligand, tris(4-phenylphosphinato-3-methyl-3-azabutyl)amine (H_3ppma), with the lanthanides have been investigated. H_3ppma forms mono- and bis(ligand) complexes when $Ln = Sm - Lu$. The formation constants of the Lu ($\log K_1 = 1.79$, $-\log K_2 = 4.40$) and the Yb ($\log K_1 = 2.25$, $\log K_2 = 4.42$) complexes were determined in aqueous solution at pH = 1.5 using a ^{31}P NMR spectroscopic method. The bis(ligand) complex is highlighted by the molecular structure of the lutetium complex $[Lu(H_3ppma)_2](NO_3)_3 \cdot 3H_2O$ ($C_{60}H_{96}LuN_{11}O_{24}P_6$), which has been solved by X-ray methods; the complex crystallizes in the trigonal space group $R\bar{3}c$, $a = 19.060(1) \text{ \AA}$, $c = 36.395(3) \text{ \AA}$, $Z = 6$. The structure was solved by Patterson methods and was refined by full-matrix least-squares procedures to $R = 0.024$ ($R_w = 0.040$) for 2061 reflections with $I > 3(I)$. The structure of the bis-complex showed the ligand to coordinate in a tridentate manner through the three phosphinate oxygens, resulting in a bicapped octahedral structure of exact S_6 symmetry, which is preserved in solution as shown by 1H and ^{31}P NMR spectroscopies (CD_3OD , $DMSO-d_6$).

The ligand H_3ppma has been shown to form S_6 symmetric bicapped bis(ligand) complexes with the lanthanides, (as seen in the X-ray crystal structure of the lutetium complex, and in solution NMR studies) whereby it binds as a tridentate ligand exclusively via the phosphinato groups. These complexes are isostructural with those obtained with the group 13 metals and similar to those obtained when the oxygen donor is phenolato.

References

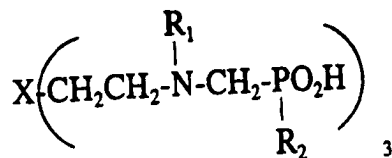
1. (a) Perl, D.P. *Environ. Health Perspect.* **1985**, 63, 149.
(b) Crapper-McLachlan, D.R. *Neurobiol. Aging* **1986**, 7, 525.
- 5 (c) Liss, L. *Aluminum Neurotoxicity*; Pathotox Publishers: Park Forest, IL, 1980.
2. (a) Welch, M.J.; Moerlein, S.M. In *Inorganic Chemistry in Biology and Medicine*; Martell, A.E., Ed.; American Chemical Society: Washington, DC, 1980; p. 121.
- 10 (b) Green, M.A.; Welch, M.J. *Nucl. Med. Biol.* **1989**, 16, 435.
(c) Zhang, Z.; Lyster, D.M.; Webb, G.A.; Orvig, C. *Nucl. Med. Biol.* **1992**, 19, 327.
3. (a) Martin, R.B.; Richardson, F.S. *Q. Rev. Biophys.* **1979**, 12, 181.
(b) Meares, C.F.; Wensel, T.G. *Acc. Chem. Res.* **1984**, 17, 202.
- 15 (c) *Lanthanide Probes in Life, Chemical, and Earth Sciences*; Bunzli, J.-C.G.; Choppin, G.R., Eds.; Elsevier: Amsterdam, 1989.
(d) Bunzli, J.-C.G. *Inorg. Chim. Acta* **1987**, 139, 219.
(e) Horrocks, W.D.J.; Albin, M. *Prog. Inorg. Chem.* **1984**, 31, 1.
(f) Gupta, R.K.; Gupta, P.J. *J. Mag. Reson.* **1982**, 47, 344.
- 20 (g) Pike, M.M.; Springer, C.S. *J. Mag. Reson.* **1982**, 46, 348.
(h) Sherry, A.D.; Geraldès, C.F.G.C.; Cacheris, W.P. *Inorg. Chim. Acta* **1987**, 139, 137.
4. Lauffer, R.B. *Chem. Rev.* **1987**, 87, 901.
5. (a) Liu, S.; Wong, E.; Karunaratne, V.; Rettig, S.J.; Orvig, C. *Inorg. Chem.* **1993**, 32, 1756.
- 25 (b) Liu, S.; Wong, E.; Rettig, S.J.; Orvig, C. *Inorg. Chem.* **1993**, 32, 4268.
(c) Liu, S.; Rettig, S.J.; Orvig, C. *Inorg. Chem.* **1992**, 31, 5400.
(d) Liu, S.; Gelmini, L.; Rettig, S.J.; Thompson, R.C.; Orvig, C. *J. Amer. Chem. Soc.* **1992**, 114, 6081.
- 30

- (f) Berg, D.J.; Rettig, S.J.; Orvig, C. *J. Amer. Chem. Soc.* 1997, 119, 2528.
- 5 (g) Smith, A.; Rettig, S.J.; Orvig, C. *Inorg. Chem.* 1998, 27, 3929.
6. Caravan, P.; Orvig, C. *Inorg. Chem.* 1997, 36, 236-248.
7. Caravan, P.; Hedlund, T.; Liu, S.; Sjöberg, S.; Orvig, C. *J. Am. Chem. Soc.* 1995, 117, 11230.
8. Lowe, M.P.; Rettig, S.J.; Orvig, C. *J. Am. Chem. Soc.* 1996, 118, 10446.
- 10 9. Glasoe, P.K.; Long, F.A. *J. Phys. Chem.* 1960, 64, 188.
10. Bertini, I.; Luchinat, C. *NMR of Paramagnetic Molecules in Biological Systems*; Benjamin/Cummings: Menlo Park, 1986; Vol. 3.
11. Gran, G. *Acta Chem. Scand.* 1950, 4, 559.
- 15 12. Motekaitis, R.J.; Martell, A.E. *Can. J. Chem.* 1982, 60, 2403.
13. *teXsan*: Crystal Structure Analysis Package (1985 & 1992). Molecular Structure Corporation, The Woodlands, TX.
14. *International Tables for X-Ray Crystallography*, Vol. IV. Kynoch Press, Birmingham, England, 1974. pp. 99-102.
- 20 15. *International Tables for Crystallography*, Vol. C. Kluwer Academic Publishers, Boston, 1992. pp. 200-206.
16. Shannon, R.D. *Acta. Crystallogr.* 1976, A32, 751.
17. Peters, J.A.; Huskens, J.; Raber, D.J. *Prog. NMR Spectrosc.* 1996, 28, 283.
- 25 18. Figgis, B.N. *Introduction to Ligand Fields*; Robert E. Krieger Publishing Co.: Malabar, Florida, 1986.
19. Golding, R.M.; Halton, M.P. *Aust. J. Chem.* 1972, 25, 2577.
20. Pinkerton, A.A.; Rossier, M.; Spiliadis, S. *J. Magn. Reson.* 1985, 64, 420.
- 30 21. Bleaney, B. *J. Magn. Reson.* 1972, 8, 91.

22. Bleaney, B.; Dobson, C.M.; Levine, B.A.; Martin, R.B.; Williams, R.J.P.; Xavier, A.V. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
23. Golding, R.M.; Pyykko, P. *Mol. Phys.* **1973**, 26, 1389.
24. Reilley, C.N.; Good, B.W.; Allendoerfer, R.D. *anal. Chem.* **1976**, 48, 1446.
- 5 25. Alpoim, M.C.; Urbano, A.M.; Geraldies, C.F.G.C.; Peters, J.A. *J. Chem. Soc. Dalton Trans.* **1992**, 463.
26. Huskens, J.; Kennedy, A.D.; van Bekkum, H.; Peters, J. *J. Amer. Chem. Soc.* **1995**, 117, 375.
- 10 27. Huskens, J.; Peters, J.A.; van Bekkum, H.; Choppin, G.R. *Inorg. Chem.* **1995**, 34, 1756.
28. Peters, J.A.; Kieboom, A.P.G. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 381.
29. Helm, L.; Foglia, F.; Kowall, T.; Merbach, A.E. *J. Phys.: Condens. Matter* **1994**, 6, A137.
- 15 30. Reuben, J.; Fiat, D. *J. Chem. Phys.* **1969**, 51, 4909.
31. Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; John Wiley & Sons: New York, 1973.
32. Blokzijl, W.; Engberts, J.B.F.N. *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1545.
- 20 33. Hancock, R.D.; Martell, A.E. *Chem. Rev.* **1989**, 89, 1875.

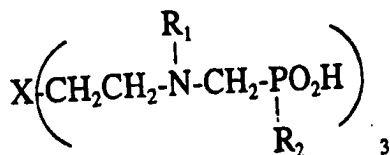
1. An amine phosphinate tripodal ligand of the formula:

5



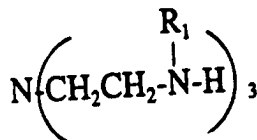
- 10 wherein X is N, CH, C₂H₅, C₃H₅, or other alkyl, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and when X is N, R₂ is CH₃, CH₂OH, other alkyl, substituted alkyl, or aryl, and when X is CH, C₂H₅, C₃H₅, or other alkyl, R₂ is C₆H₅, CH₃, CH₂OH, or other alkyl, substituted alkyl or aryl, and physiologically compatible salts and derivatives thereof.

- 15 2. A process of preparing an amine phosphinate tripodal ligand of the formula:

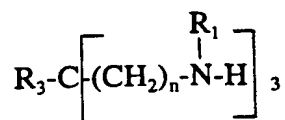


20

- wherein X is N, CH, C₂H₅, C₃H₅, or other alkyl, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and when X is N, R₂ is CH₃, CH₂OH, other alkyl, substituted alkyl, or aryl, and when X is CH, C₂H₅, C₃H₅, or other alkyl, R₂ is C₆H₅, CH₃, CH₂OH, or other alkyl, substituted alkyl or aryl, and physiologically compatible salts and derivatives thereof, which comprises
- 25 (a) reacting an appropriate tripodal amine of the formula:

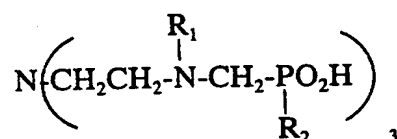


30 or

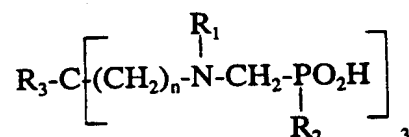


- wherein n is 1 or 2, R₁ is H, CH₃, C₂H₅, or other alkyl or benzyl; and R₃ is H, CH₃, C₂H₅, or other alkyl; with H₂P(R₂)O₂ and CH₂O or (CH₂O)_m, wherein R₂ is H, C₆H₅, CH₃, other alkyl, substituted alkyl, or aryl, and m is 2 or greater; or
 5 (b) converting the R₂ group of one amine phosphinate tripodal ligand to another R₂ group by using formaldehyde or paraformaldehyde.

- 10 3. A process as claimed in claim 2 of preparing an amine phosphinate tripodal ligand of the formula:



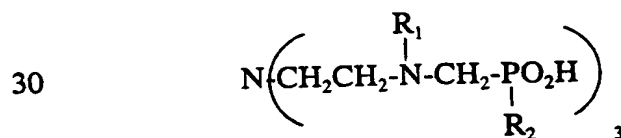
15 or



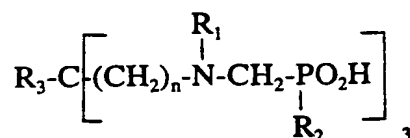
- 20 wherein n is 1 or 2, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and R₃ is H, CH₃, C₂H₅ or other alkyl; and R₂ is CH₂OH, and physiologically compatible salts and derivatives thereof, which comprises converting an amine phosphinate tripodal ligand wherein R₂ is H to an amine phosphinate tripodal ligand wherein R₂ is CH₂OH by reacting with formaldehyde or paraformaldehyde.

25

4. A process of chelating a metal ion which comprises complexing the metal ion with an amine phosphinate tripodal ligand of the formula:



or



5

wherein n is 1 or 2, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and R₃ is H, CH₃, C₂H₅ or other alkyl; and R₂ is C₆H₅, CH₃, CH₂OH, other alkyl, substituted alkyl, or aryl, except when R₂ is C₆H₅, the metal ion excludes Al, Ga, In, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu.

10

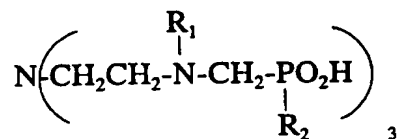
5. A process as claimed in claim 4 wherein the metal ion is selected from the group consisting of Tc, Re, the group 13 metals and rare earths.

6. A process of chelating a trivalent metal ion of the group 13 metals and the rare earths as claimed in claim 4 which comprises complexing any one of the group 13 metals, Al, Ga and In, and any one of the rare earths, Sc, Y, La, Ce, Pr, Nd, Pm, Sm, Eu Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, with the amine phosphinate tripodal ligand.

7. A process as claimed in claim 4 wherein any one of the group 13 metals, Al, Ga and In is complexed with the amine phosphinate tripodal ligand.

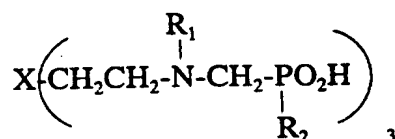
8. A process as claimed in claim 4 wherein any one of the lanthanide metals, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, is complexed with the amine phosphinate tripodal ligand.

9. A process as claimed in claim 4 wherein the amine phosphinate tripodal ligand is of the formula:



- 5 wherein n is 1 or 2, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and R₂ is C₆H₅, CH₃, CH₂OH, other alkyl, substituted alkyl, or aryl, and the metal ion is Tc, Re, Sc, Y, Ce, Pr or Pm.

10. A chelate comprising a metal ion and an amine phosphinate tripodal
10 ligand of the formula:



15

- wherein X is N, CH, C₂H₃, C₃H₅, or other alkyl, R₁ is H, CH₃, C₂H₅ or other alkyl or benzyl; and when X is N, R₂ is CH₃, CH₂OH, other alkyl, substituted alkyl, or aryl, and when X is CH, C₂H₃, C₃H₅, or other alkyl, R₂ is C₆H₅, CH₃, CH₂OH, or other alkyl, substituted alkyl or aryl, and physiologically compatible
20 salts and derivatives thereof.

11. A chelate as claimed in claim 10 wherein the metal ion is selected from the group consisting of Tc, Re, the group 13 metals and the rare earths.

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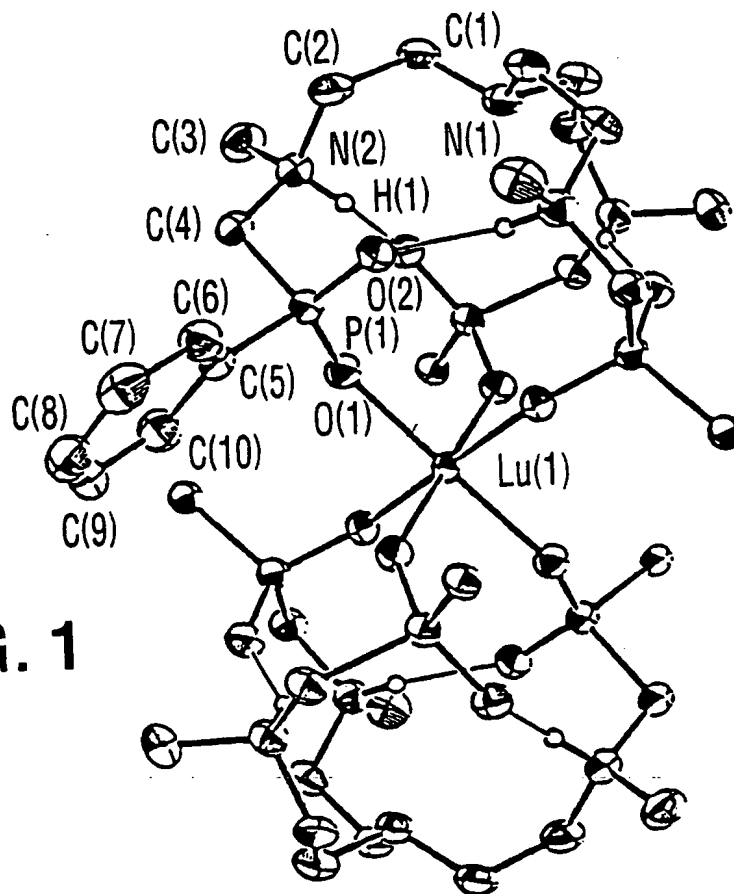


FIG. 1

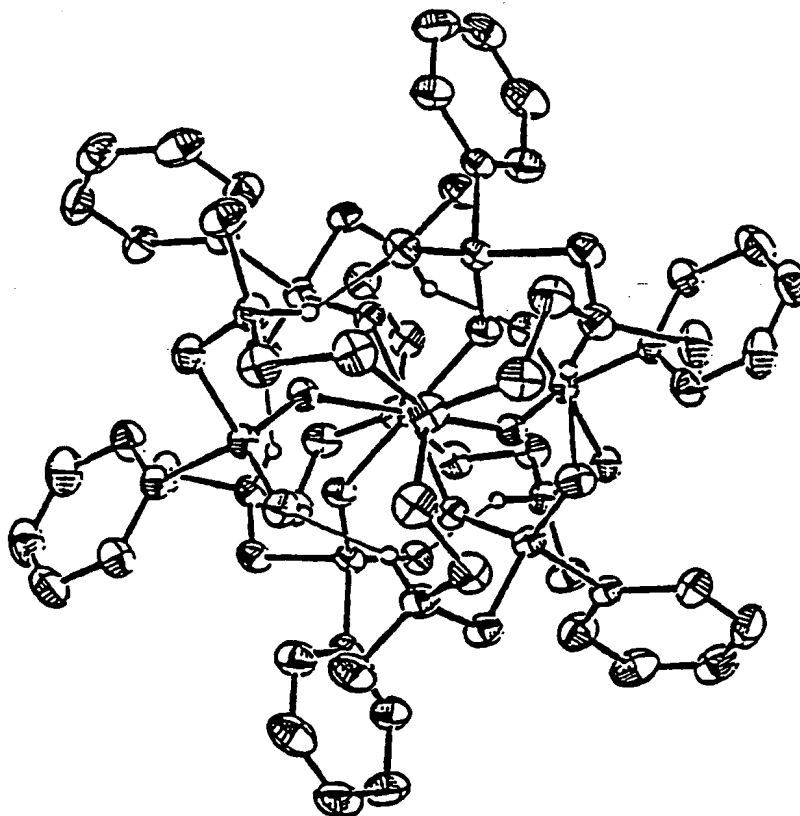


FIG. 2

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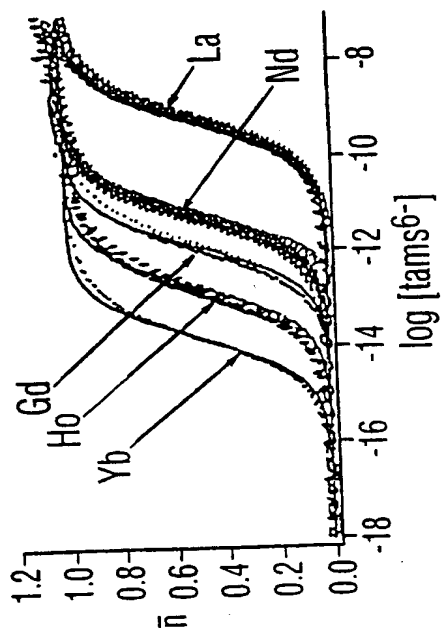


FIG. 4a

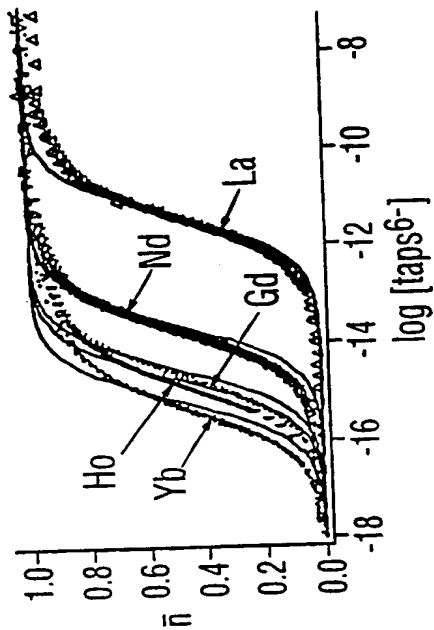


FIG. 4b

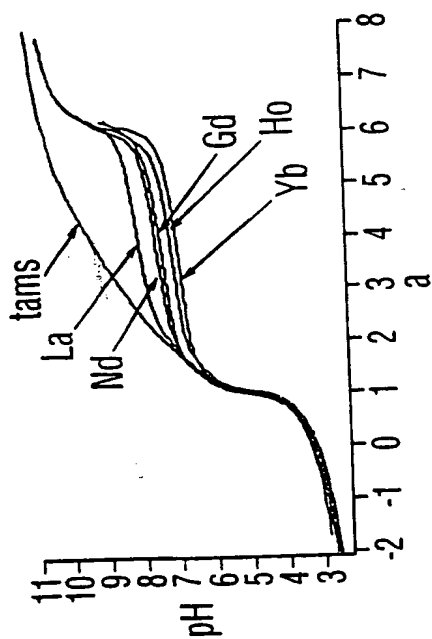


FIG. 3a

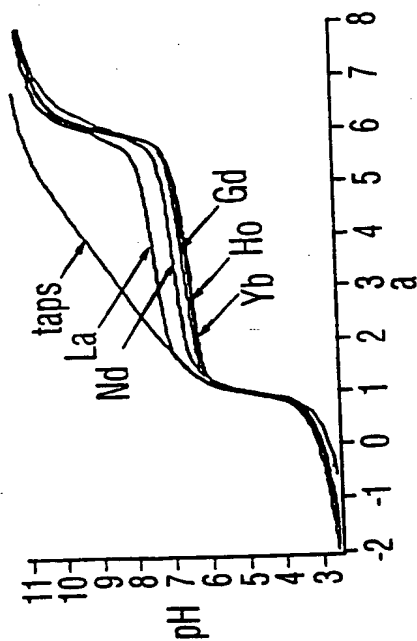
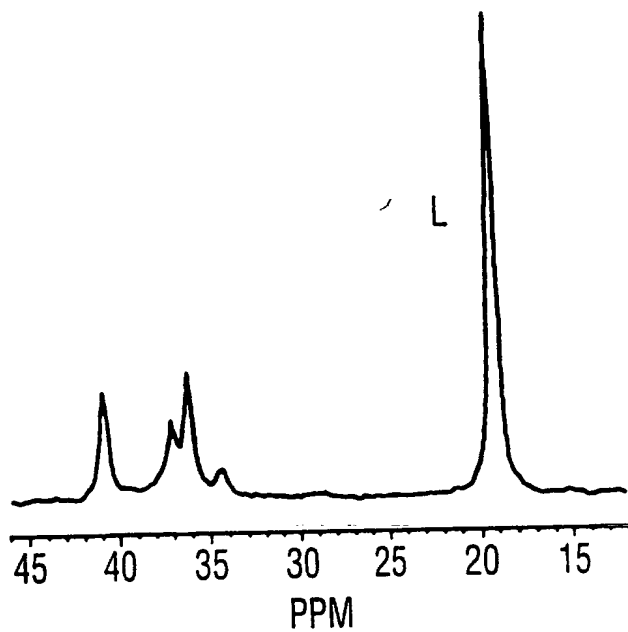
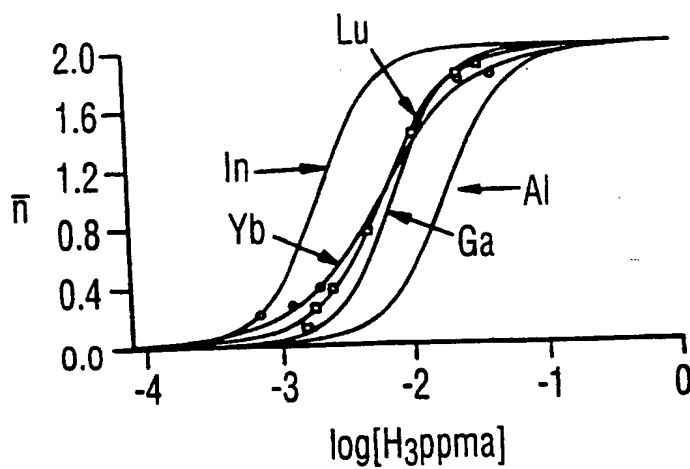
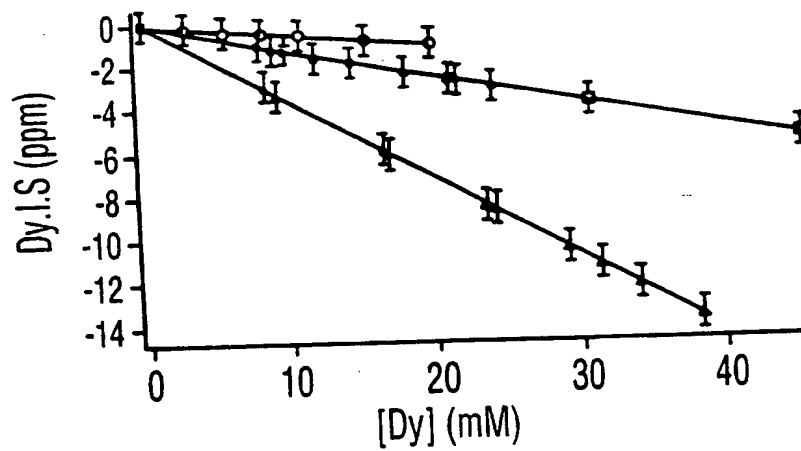
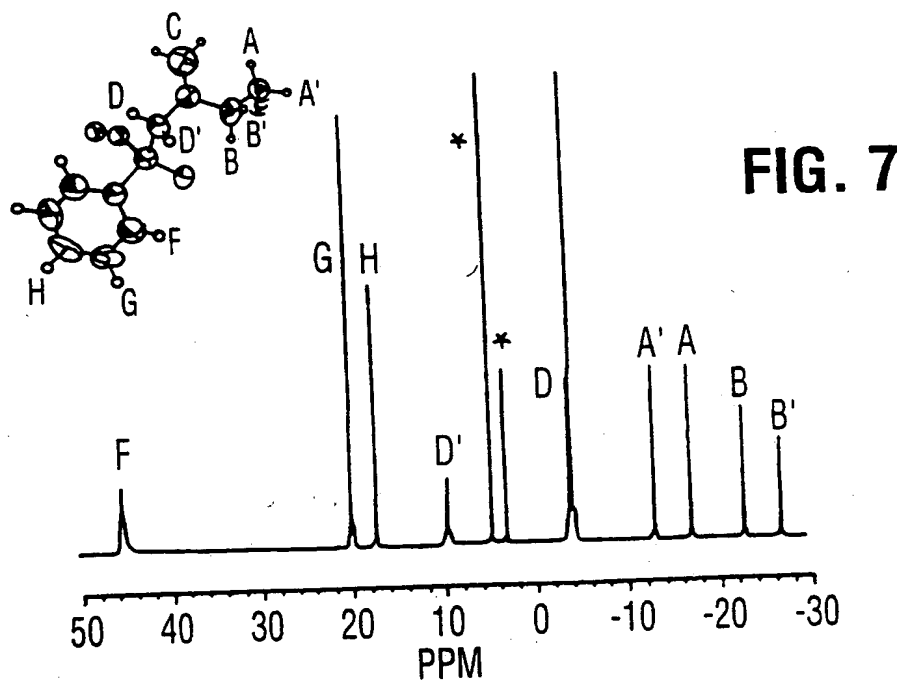


FIG. 3b

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**FIG. 5****FIG. 6**

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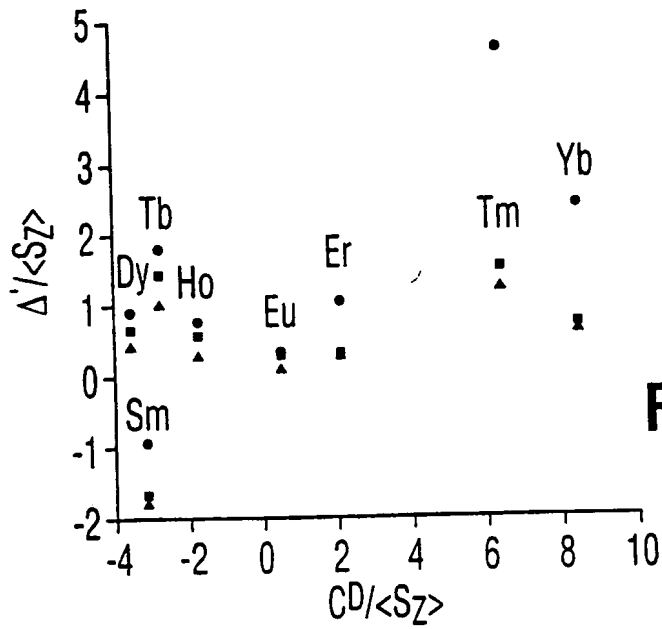


FIG. 8a

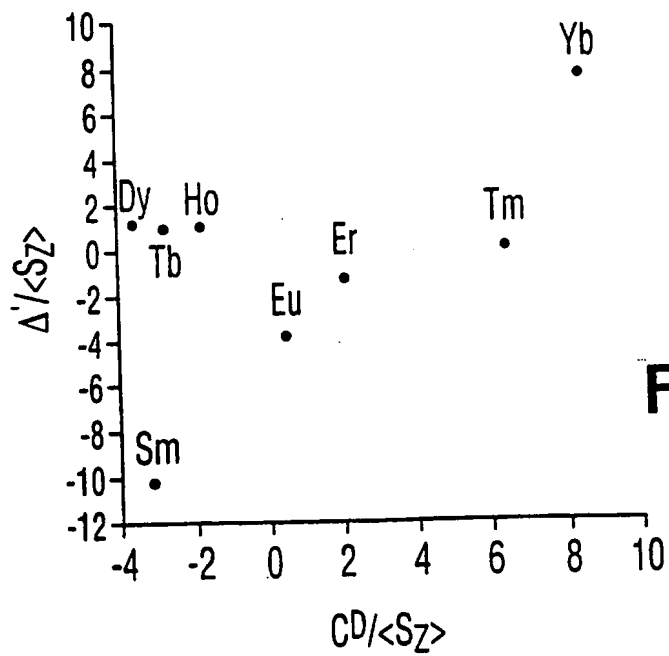
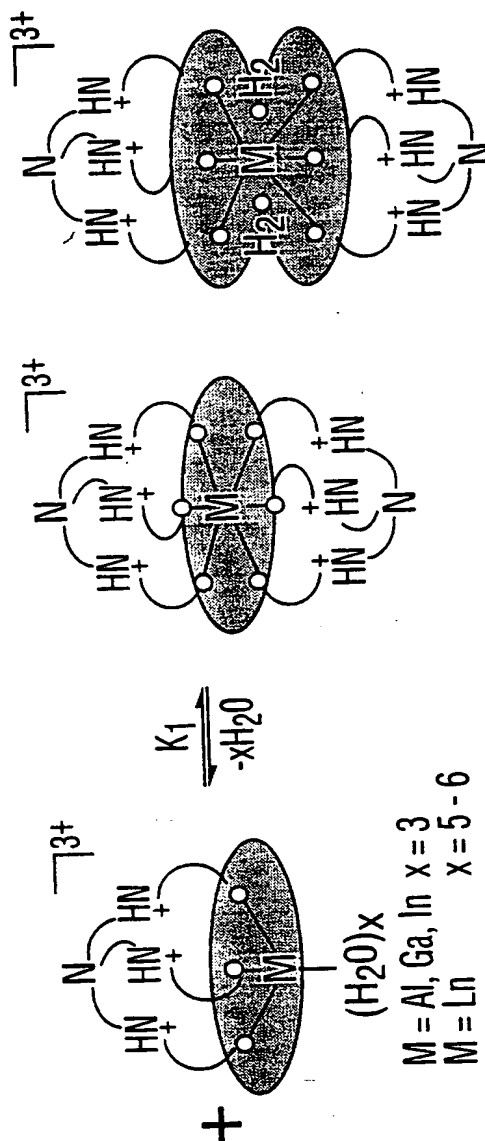
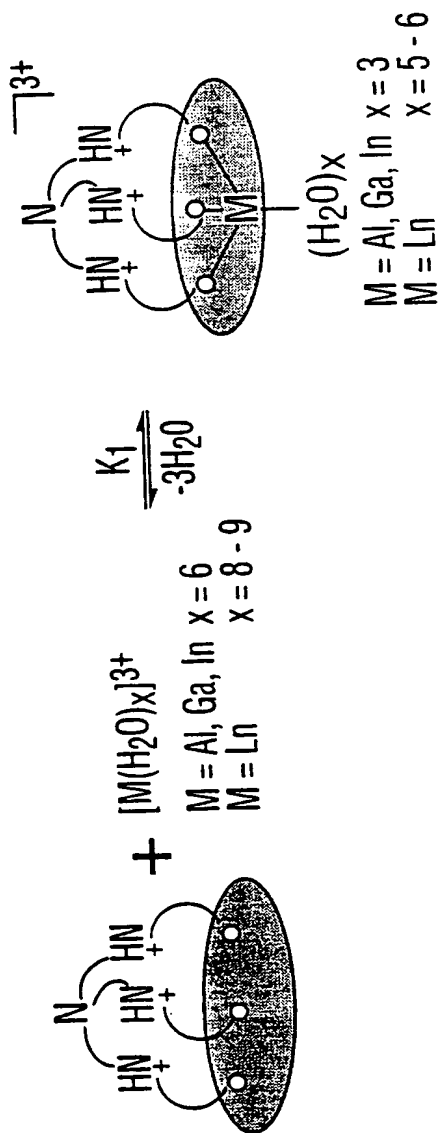


FIG. 8b

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Al, Ga, In and smaller Lanthanides

smaller Lanthanides

FIG. 10

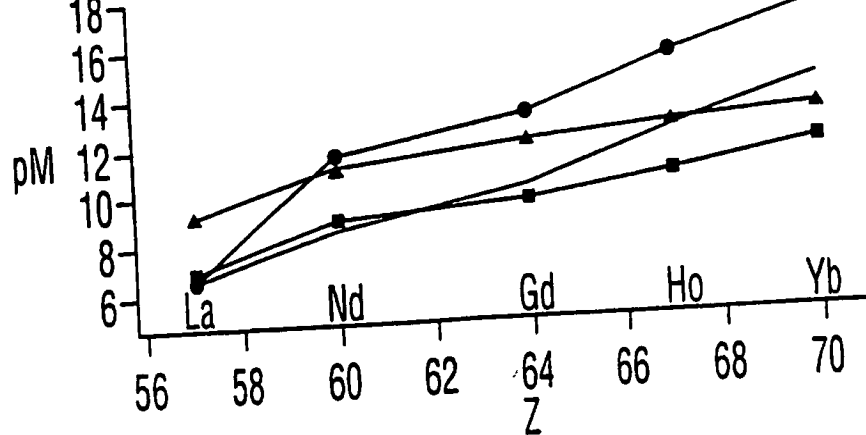


FIG. 11

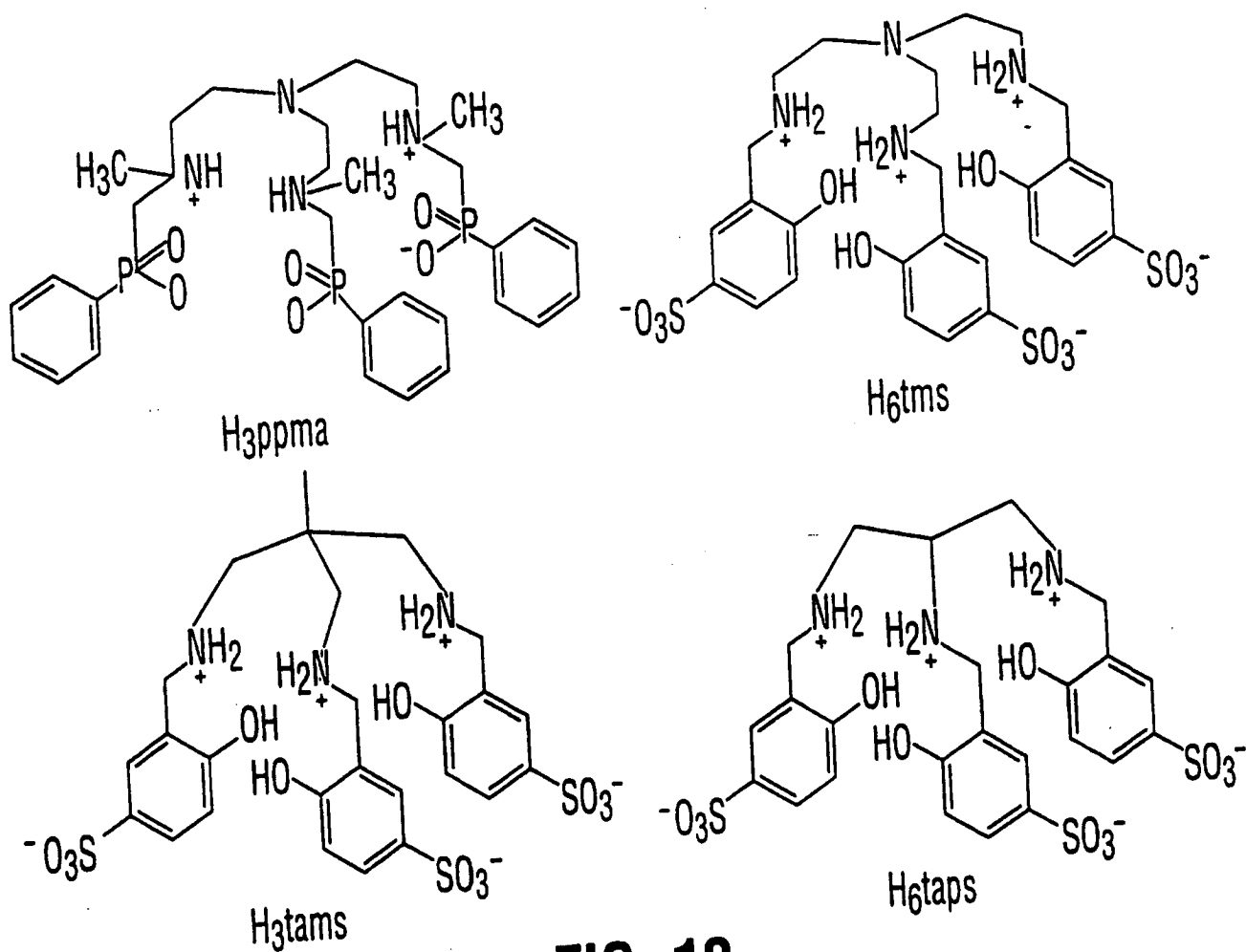


FIG. 12

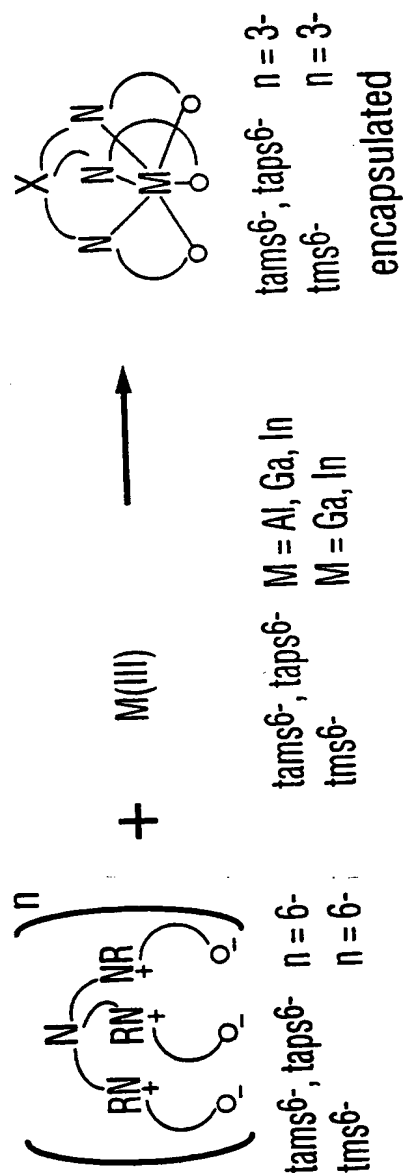
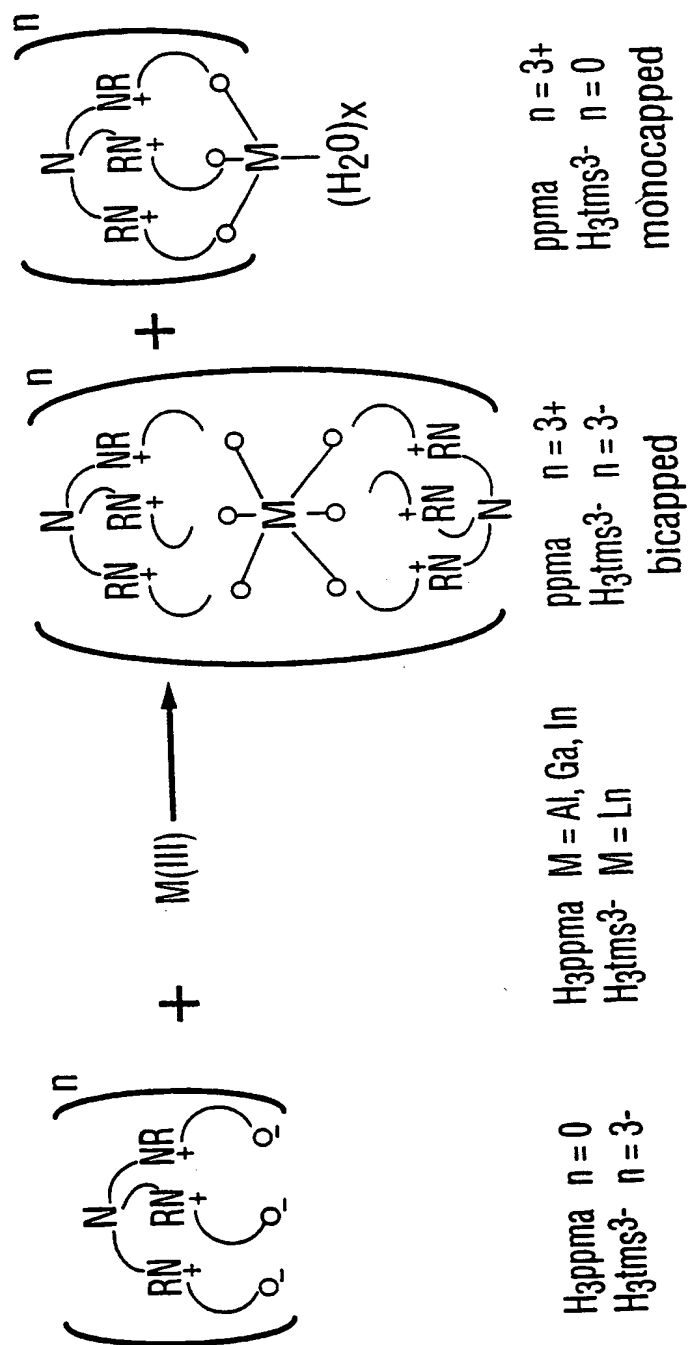


FIG. 13

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07F9/30

C07F9/48

A61K51/04

A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LOWE M P ET AL: "Highly Symmetric Group 13 Metal-Phosphinato Complexes: Multinuclear NMR (27Al, 31P, 71Ga) Determination of Stability Constants at Low pH" J. AM. CHEM. SOC. (JACSAT,00027863);96; VOL.118 (43); PP.10446-10456, - 30 October 1996 XP002078541 University of British Columbia;Department of Chemistry; Vancouver; V6T 1Z1; BC; Can. (CA) cited in the application see the whole document ---	1-11
Y	WO 95 01124 A (MALLINCKRODT MEDICAL, INC.) 12 January 1995 see the whole document --- -/--	1-11

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Date of the actual completion of the international search

24 September 1998

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>LOWE M P ET AL: "Tightening the Hydrophobic Belt: Effects of Backbone and Donor Group Variation on Podand Ligand Complexes of the Lanthanides"</p> <p>INORG. CHEM. (INOCAL,00201669);98; VOL.37 (7); PP.1637-1647, - 6 April 1998</p> <p>XP002078542</p> <p>University of British Columbia;Department of Chemistry; Vancouver; V6T 1Z1; BC; Can. (CA)</p> <p>see the whole document</p> <p>-----</p>	1-11

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501124 A	12-01-1995	US 5405601 A	11-04-1995
		AU 7116694 A	24-01-1995
		EP 0711180 A	15-05-1996
		JP 9500115 T	07-01-1997
		US 5565184 A	15-10-1996